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# Synthesis of Different Heterocyclic Compounds of Pharmaceutical Relevance


**Musharraf Naveed Khan**

A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Institute of Materials, Medicines and Molecular Sciences, Division of Chemistry,

University of Huddersfield

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*I would like to dedicate this thesis to my father, Muhammad Ashraf Khan, who motivated me to study natural sciences and worked really hard to make my career, till he breathed his last, his dedication and commitment cannot be described in words, my mother who made many sacrifices and had to face many hardships and tough situations to support me and make my career, and to my brother Farrukh Nadeem Khan for all his motivation, affection and help throughout my studies.*

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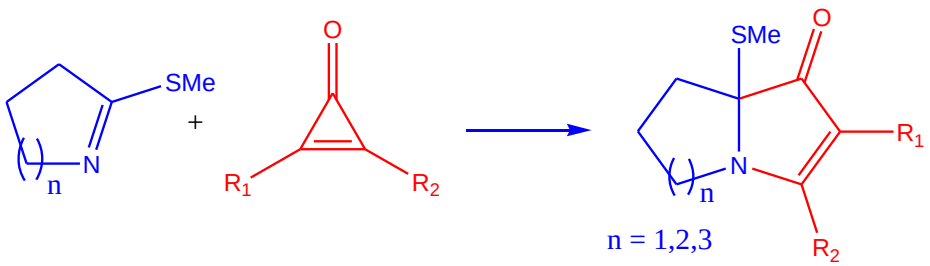
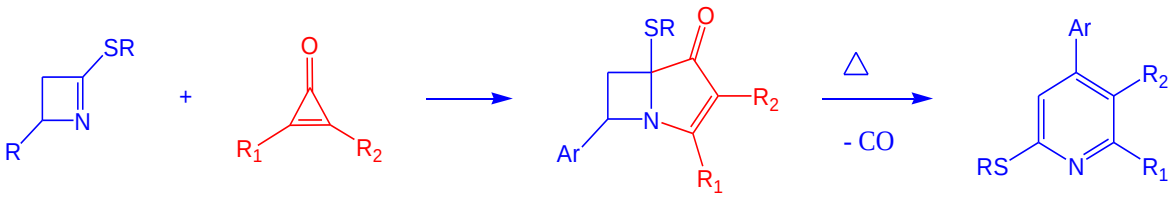
## Abstract

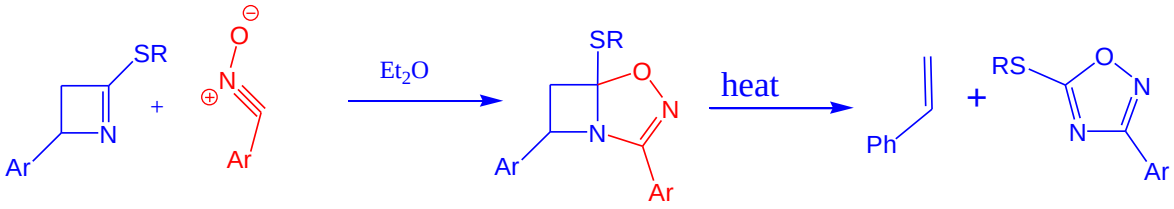
This thesis describes the synthesis of different cyclic imines and the exploration of their reactivity with cyclopropenones and 1,3-dipoles, as well as an investigation of the chemistry of the products. The synthesis of biologically and pharmaceutically important heterocyclic natural product analogues, such as the pyrroloazepines, indolizidines and pyrrolizidines has been achieved using a cycloaddition reaction between cyclic imidates and cyclopropenones.



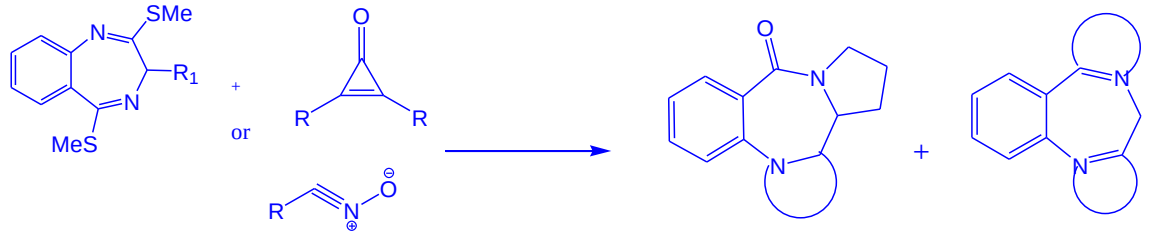

A new route to pyridines has been developed using the generation of a proposed 3-azacyclopentadienone as the key step. The 3-azacyclopentadienones are generated by using boiling toluene to induce a [2+2]-cycloreversion in a series of azabicyclo[3.2.0]hept-2-en-4-ones. Regiospecific Diels-Alder reaction of the intermediate 3-azacyclopentadienone with a styrene is followed by chelotropic extrusion of carbon monoxide and loss of hydrogen to give the pyridine.



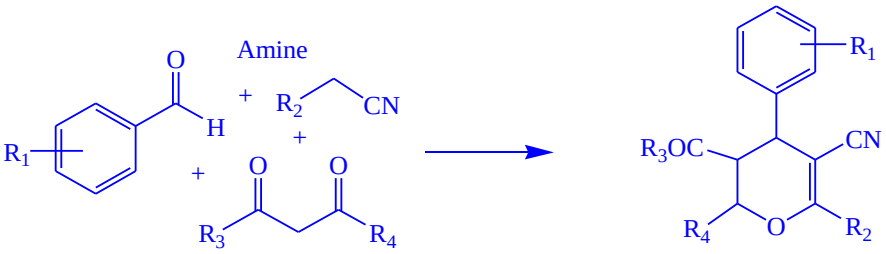

The process is similar to the well-known process by which benzenes are accessed from cyclopentadienones. The azabicyclo[3.2.0]hept-2-en-4-ones were available from the reaction of cyclopropenones with 1-azetines, where cyclopropenones behave as an all carbon 1,3-dipole equivalents. Using the same methodology 1,3-dipolar cycloaddition of nitrile oxides to 4-aryl-2-alkylthio-1-azetines afforded a series of oxadiazabicyclo[3.2.0]heptenes as single diastereoisomers. Heating these cycloadducts in toluene resulted in an overall [2+2]-cycloreversion to give 5-alkylthio-3-aryl-1,2,4-oxadiazoles.




Cycloaddition reactions of a series of benzodiazepines were also studied. The benzodiazepines were formed using literature methods and converted to cyclic imines with the help of Meerwein's reagent. Reactions between such cyclic imines and cyclopropenones and 1,3-dipoles were attempted to produce tricyclic and tetracyclic benzodiazepine analogues.




Finally, some multicomponent reactions of aryl aldehydes with cyanides and 1,3-dicarbonyl compounds were investigated to produce fully substituted heterocyclic compounds like dihydropyridines and pyrans with substituents suitable for intramolecular cyclization and imine formation. The main substituent of interest was the azide group as this had been used in section 2.3.3.1.2 & 2.3.3.1.3 in this thesis.




## Research Output

1. Pyridines from azabicyclo[3.2.0]hept-2-ene-4-ones through a proposed azacyclopentadienone. Karl Hemming*, Musharraf N Khan, Vishnu V. R. Kondakal, Arnaud Pitard, M. Ilyas Qamar and Craig Rice. *Org. Lett.*, **2012,** *14*, 1, 126-129**.**
2. 1,2,4-Oxadiazoles from cycloreversions of oxadiazabicyclo[3.2.0]heptenes: 1-azetines as thiocyanate equivalents. Karl Hemming,* Musharraf N. Khan, Paul A. O'Gorman, Arnaud Pitard. *Tetrahedron*, *69*, **2013**, 1279-1284.
3. Synthesis of tetrazolo- and oxadiazolo-derivatives of the DNA-interactive pyrolo[2,1,c][1,4]benzodiazepines and pyrrolobenzothiadiazepines. Karl Hemming*, Chris S Chambers, Heidi Joao, Musharraf N Khan, Nilesh Patel. *Tetrahedron,* **2013**, submitted.

# Abbreviations

| | |
|---|---|
| **Å** | Angstrom |
| **Ac** | acyl |
| **ACN** | acetonitrile |
| **ala** | alanine |
| **aq.** | aqueous |
| **Ar** | aromatic |
| **b** | broad |
| **Bn** | benzyl |
| **Boc** | butyloxycarbonyl |
| **b.p.** | boiling point |
| **bs** | broad singlet |
| **CSI** | *N*-chlorosulfonyl isocyanate |
| **Conc.** | concentrated |
| **d** | doublet |
| **DBU** | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| **DCM** | dichloromethane |
| **dd** | doublet of doublet |
| **ddd** | doublet of doublet of doublets |
| **DDQ** | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| **de** | diastereomeric excess |
| **DEPT** | distortionless enhancement by polarisation transfer |
| **DMAD** | dimethyl acetylene dicarboxylate |
| **DMF** | *N,N*-dimethylformamide |
| **DMSO** | dimethylsulfoxide |
| **DPP** | diphenylcyclopropenone |
| **EA** | ethyl acetate |
| **EAA** | ethylacetoacetate |
| **EWG** | electron withdrawing group |
| **h** | hour(s) |
| **HMBC** | heteronuclear multiple bond connectivity |
| **HRMS** | high resolution mass Spectrometry |
| **HSQC** | heteronuclear single quantum Coherence |
| **lit.** | literature |
| **lys.** | lycine |
| **m** | medium (IR), multiplet (NMR |
| **mg** | milligramme |
| **mmol** | millimole |
| **min.** | minute(s) |
| **m.p.** | melting point |
| **Ms** | mesylate |
| **MS** | mass spectrometry |
| **MW** | molecular weight |
| **NMR** | nuclear magnetic resonance |
| **NOE** | nuclear Overhauser effect |
| **PE** | petroleum ether |
| **Ph** | phenyl |
| **ppm** | parts per million |
| **q** | quartet |
| **rt** | room temperature |
| **s** | strong (IR), singlet (NMR) |
| **t** | triplet (NMR) |
| **td** | triplet of doublets |
| **TFA** | trifluoroacetic acid |
| **THF** | tetrahydrofuran |
| **TLC** | thin layer chromatography |
| **Ts** | tosyl |
| **UV** | ultraviolet |

| | |
|---|---|
| **vs** | very strong (IR) |
| **w** | weak (IR) |
| **XRD** | X-ray diffraction |

# *Chapter 1;*

# *Introduction*

# 1. Introduction

This thesis will describe new approaches to the synthesis of 1,2,4-oxadiazoles and pyridines, an attempt to use benzodiazepines as cyclic imines and the use of *o*-azidobenzaldehyde in multicomponent reactions. Short introductions to 1,2,4-oxadiazoles, pyridines and multicomponent reactions of aryl aldehydes are therefore included.

## 1.1 1,2,4-oxadiazoles

Oxadiazoles are five-membered heterocycles containing two carbon atoms, two nitrogen atoms and one oxygen atom. These compounds are of considerable importance in different areas of pesticide and medicinal chemistry as well as polymer and material sciences[1]. Oxadiazoles have been proved to have a large impact on multiple drug discovery programmes across different disease areas including cancer[2], inflammation[3], diabetes[4], obesity[5] and infection[6]. Raltegravir **1**, an oxadiazole containing compound and antiretroviral drug for the treatment of HIV infection[7], has been recently launched into the market. Furthermore, a number of compounds containing an oxadiazole ring are at the final stage of clinical trials e.g. zibotentan **2** as an anticancer agent[8] and ataluren **3** for the treatment of cystic fibrosis[9].

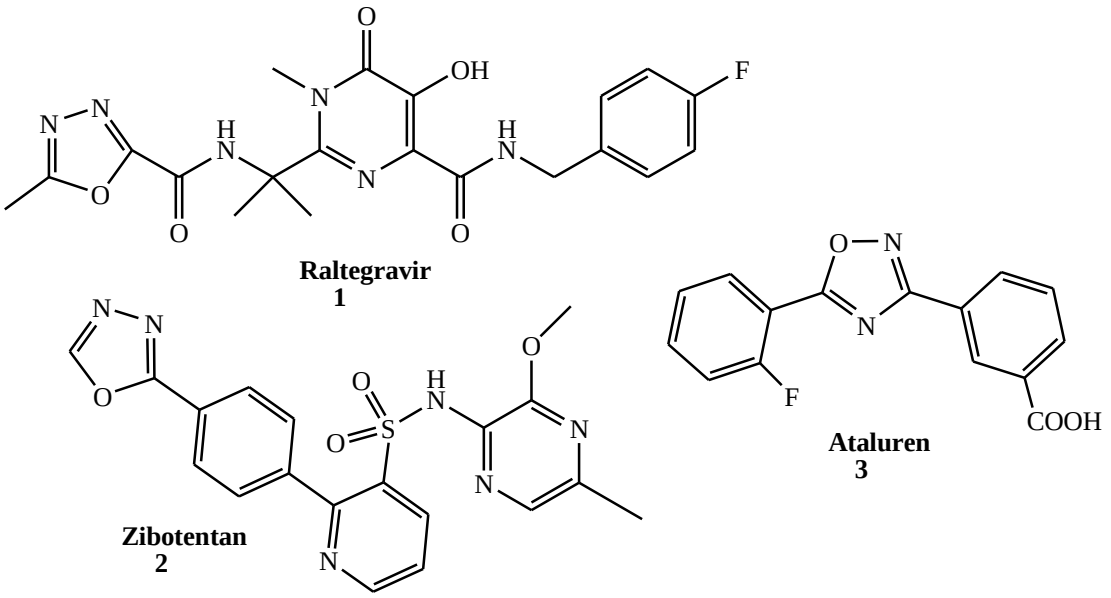



**Fig. 1.1**

There are several reasons behind the introduction of oxadiazoles into the drug discovery programmes. They have been used as a replacement of carbonyl compounds like esters, amides, carbamates and hydroxamic esters. Oxadiazoles have been used as a vital part of the pharmacophore, contributing towards ligand binding[10], and in some cases they act as a flat aromatic linker to place substituents in appropriate orientations[11]. These moieties have also been used to modulate molecular properties by placing them in the periphery of the molecule[12].

Oxadiazole rings can exist in three different regioisomeric forms as 1,2,4-oxadizole **4**, 1,3,4-isomer **5** and the 1,2,5-isomer **6**. This thesis will focus only on 1,2,4-oxadiazoles.

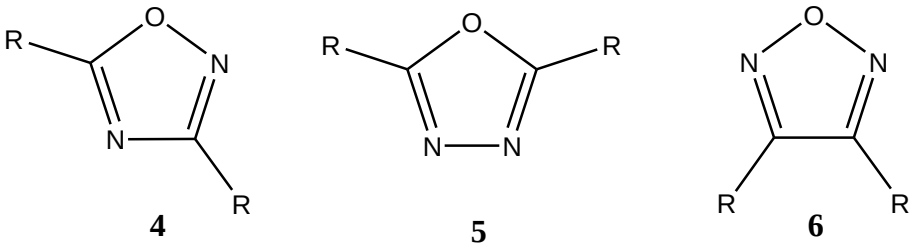


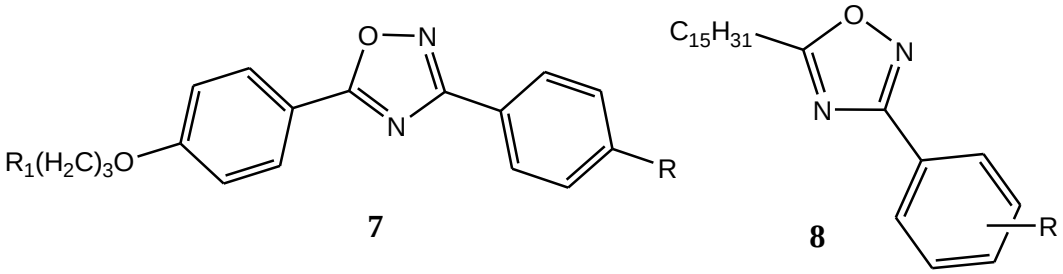

**Fig. 1.2**

### 1.1.1. Bioactivity of 1,2,4-oxadiazoles

#### 1.1.1.1. Antiinflammatory and antiasthmatic agents

1,2,4-Oxadiazoles are known to show antiinflammatory properties and one example is 5-methyl-3-phenyl-1,2,4-oxadiazole which shows properties similar to phenylbutazone[13]. Some other compounds like dual cyclooxygenase/5-lypoxygenase, coumarin and 3-phenyl-1,2,4-oxadiazole-5-carbohydrazide derivatives have been reported[3,14,15] to show antiinflammatory activities. A new class of interleukin-8 antagonists containing a 3,5-diaryl-1,2,4-oxadiazole **7** has been introduced[16] as potential antiinflammatory agents. 1,2,4-oxadiazoles having a fatty acid chain at C (5) **8** as isosters of palmitic acid derivatives show inhibition to fatty acid amide hydrolase (FAAH), with activity similar to aspirin and ibuprofen[17]. The introduction of a long chain hydrocarbon to the oxadiazole ring increases the hydrophobicity of these molecules which allows them to enter the cells more quickly and leave more slowly than

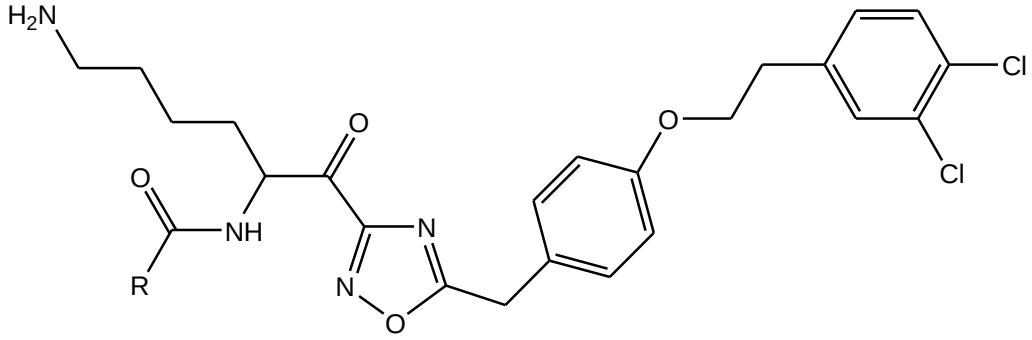
shorter alkyl chain derivatives, hence, increasing the anti-inflammatory activity of these compounds.




**7** **8**

**Fig. 1.3**

Some α-keto 1,2,4-oxadiazoles **9** have been found as inhibitors of human mast cell tryptase, an enzyme that is linked with immediate and long term effects of asthma[18].



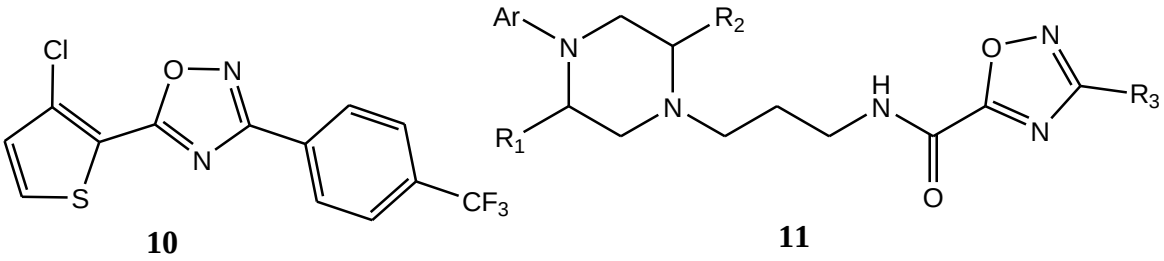

**9**

**Fig. 1.4**

### 1.1.1.2 Anti-tumoral activity

Cancer is in fact a condition consisting of more than one hundred different diseases, all causing uncontrolled growth and spread of abnormal cells. For the discovery of anti-cancer drugs, the identification of compounds acting as apoptosis inducers is of considerable interest. It has been proved by high throughput screening (HTS) assays that 1,2,4-oxadiazoles like **10** can act as apoptosis agents[2]. Moreover, structure activity relationship (SAR) of 3,5-diaryl-1,2,4-oxadiazoles has shown that changing the para-substituent of the aryl group has no effect on the activity of the compound. 3,5-Diaryl-1,2,4-oxadiazoles have been shown to induce apoptosis selectively in breast and colorectal cancer without affecting the primary

normal cells[19]. A series of 1,2,4-oxadiazoles carboxamides **11** have also been examined for inhibition to glycogen synthase kinase-3 (GSK-3) which is an important regulator of differentiation and proliferation of cells.




**10** **11**

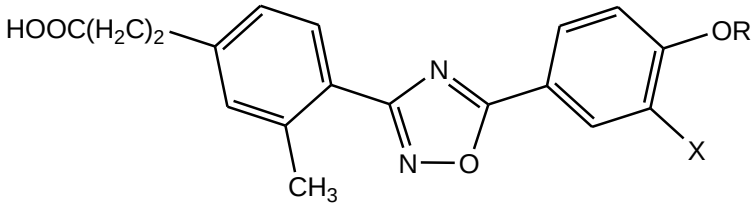
**Fig. 1.5**

1,2,4-Oxadiazole-5-thione and 1,2,4-oxadiazole-5-one are considered good bioisoesters in the hydrophilic pharmacophore of known non-steroidal androgen receptor antagonists for the treatment of prostate cancer[20]. Sulfonyl and sulfide derivatives of 1,2,4-oxadiazoles have also been tested by MTT assay on prostate cancer cells, DU-145. These compounds showed good activity on androgen independent cells PC-3 whereas on androgen dependent cells LNCaP, showed moderate activity[21]. 1,2,4-Oxadiazoles which are thiol-linked and contain electron withdrawing aryl substituents have been found active against androgen independent prostrate cancer cell-lines[21]. 1,2,4-Triazol-3-ylsulfanylmethyl-3-phenyl-1,2,4-oxadiazoles antagonize Wnt signalling and are inhibitors of tankyrases (TNKS1 and 2) that show no activity against PARP1 and 2 (poly ADPribose polymerase domains). The dysregulation of the Wnt pathway is the cause of several diseases including some cancer developments[22].

### 1.1.1.3. Immunosuppressors

Sometimes, the immune system of the body needs to be suppressed, such as in preparation for organ transplantation to avoid the rejection of donor tissue, or in treatment of auto-immune diseases such as Crohn's disease and rheumatoid arthritis. 1,2,4-Oxadiazoles have been found to be efficient mimetics for monophosphorylated tetrapeptide sequences found in SH2 domains of ZAP-70 (zeta chain associated protein kinase-70 which plays a key role in T-cell activation by its SH2 domains) and might be potential immunosuppressors[23]. Sphingosine-1-

phosphate (S1P1) receptors have been identified as targets of immunosuppressant drugs and compound **12** has shown properties as S1P1 agonist[24]. Compound **12** is an excellent S1P1 selective modulator that suppresses the development of auto-immune diseases such as multiple sclerosis and adjuvant-induced arthritis models[25].

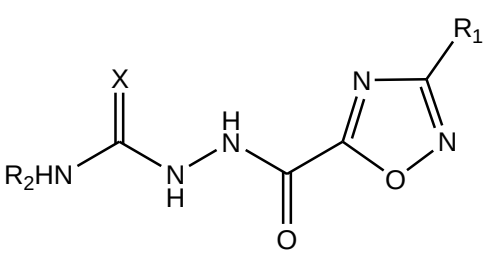



**12**

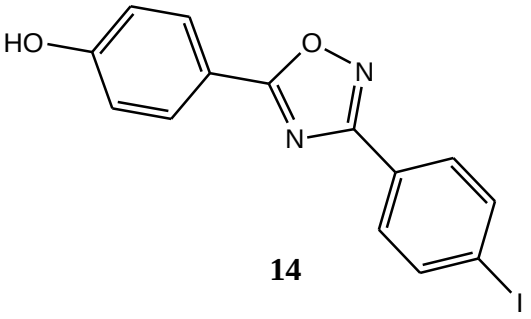
**Fig. 1.6**

### 1.1.1.4. Neuroprotective agents

Sirtuins are proteins (S1RT 1-7) which are important in age-related diseases, and a number of 1,2,4-oxadiazole carbonylaminourea derivatives **13** have shown good affinity for S1RT1 and S1RT2 in virtual based screening proving their importance for inhibitory activity in such diseases[26]. Development of new dopamine agonists represents a new approach towards therapy for Parkinson's disease. A series of 3-(5-bromo-2,3-dimethoxyphenyl)-1,2,4-oxadiazoles have been synthesized and tested as dopamine agonists and showed good results[27]. The 1,2,4-oxadiazole system has the advantage that it can replace the amide group in a series of benzamide analogues with high affinity for dopamine receptors. Another common neurodegenerative disease is Alzheimer's disease. Development of probes for *in vivo* imaging of β-amyloid plaques, formed in the brain during the early stages of disease, is an emerging research area. A series of 3,5-diaryl-1,2,4-oxadiazoles have been designed as potential probes for β-amyloid plaques and compound **14** has shown good affinity for these plaques[1]. However, these compounds have an unfavourable *in vivo* pharmacokinetic profile due to non-specific bonding, therefore, some structure modifications are needed to reduce the lipophilicity of these 1,2,4-oxadiazole derivatives[11].




**13**

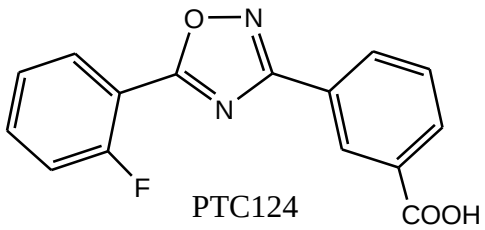



**14**

**Fig. 1.7**

### 1.1.1.5. Non-sense mutation readthrough promoters

An alteration in genetic code due to changes in a nucleotide is called a non-sense mutation. It can convert an amino acid encoding codon to a translational stop codon (UAA, UAG or UGA) in the protein coding region of mRNA which can cause premature interruption of mRNA translation and production of truncated proteins. Such mutations are responsible for diseases like cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD)[28,29]. It is of considerable importance to search for compounds which can promote the readthrough of premature stop codons and allow the synthesis of functional proteins. *Ataluren*, 3-[5-(2-fluorophenyl)-[1,2,4]-oxadiazole-3-yl]-benzoic acid **3**, also known as PTC-124, has been found to promote suppression of UGA stop codon and to correct the processing of the gene in patients who are affected by non sense mutations[30-32]. It allows the ribosome to continue the translation process to make a full length and functional protein chain, through bypassing the premature mRNA stop codon and not affecting the correct stop codons in mRNA.



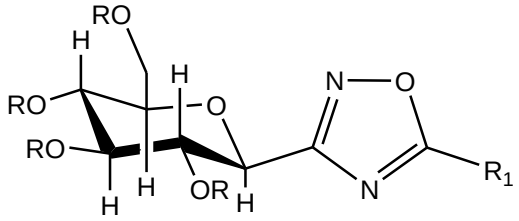

PTC124

**3**

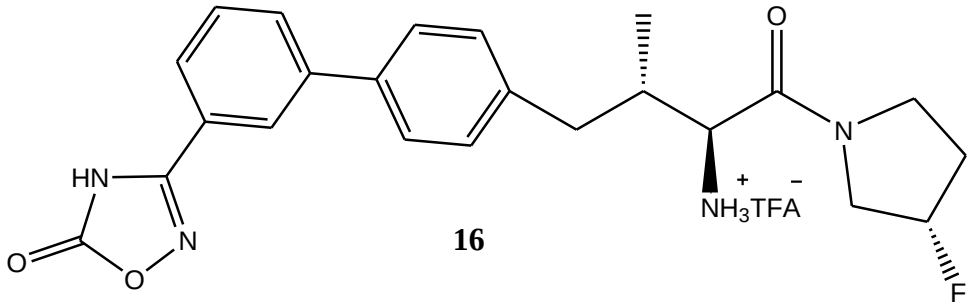
**Fig. 1.8**

### 1.1.1.6. Antidiabetic activity

Inhibition of glycogen phosphorylase (GP), which is responsible for the release of glucose-1-phosphate from glycogen, is considered as an efficient approach for the treatment of diabetes. A number of 3-β-D-glucopyranosyl-1,2,4-oxadiazoles **15** have shown inhibition against GP[33]. Inhibition of dipeptidyl peptidase-IV (DPP-IV) is another approach for treatment of diabetes, and 5-oxo-1,2,4-oxadiazole **16** has been found a potent inhibitor towards DPP-IV[34].




**15**

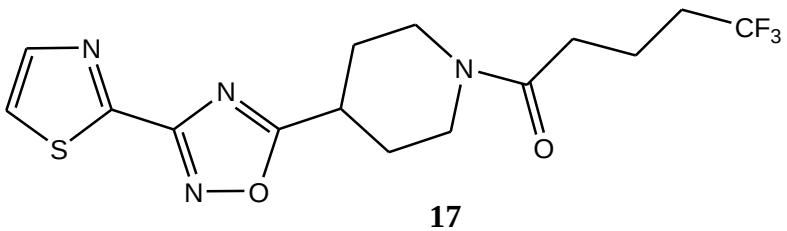



**16**

**Fig. 1.9**

### 1.1.1.7. Antimicrobial activity

1,2,4-Oxadiazoles show anti-microbial activity, for example, compound **17** is one of a series of 1,2,4-oxadiazoles that have been found as potent ethionamide boosters due to their ability to act as EthR inhibitors in the treatment of tuberculosis[35].




**17**

**Fig. 1.10**

3-Methyl-1,2,4-oxadiazole-5-yl has been used as a hydrolysis resistant grouping in HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTs) and has proved itself as the best

bioisosteric replacement for compounds with a methyl ester group expressing anti-HIV activity with submicromolar $EC_{50}$ values[36].

### 1.1.1.8. Importance of 1,2,4-oxadiazoles in materials

1,2,4-Oxadiazoles have also been found useful in materials research[1]. The recent synthesis of bent-core[37], bent-rod like[38] and H-bond induced liquid crystals[39] like compound **18** which are stable over broad temperature ranges are examples of their importance. 3-Nitro-5-substituted 1,2,4-oxadiazoles such as compound **19** have been reported as energetic, insensitive high explosives (IHEs)[40]. Pyridyl-1,2,4-oxadiazoles[41] and *bis*-1,2,4-oxadiazole[42] have been used as chelating ligands in the synthesis of $Ni^{II}$, $Cu^{II}$, $Zn^{II}$ and $Pd^{II}$ complexes, whereas, *bis*(pyridyl)-1,2,4-oxadiazole Cu (II) complexes have shown good activity as DNA groove binders[43].

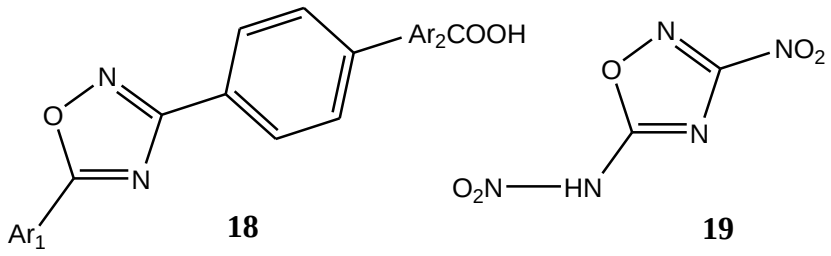
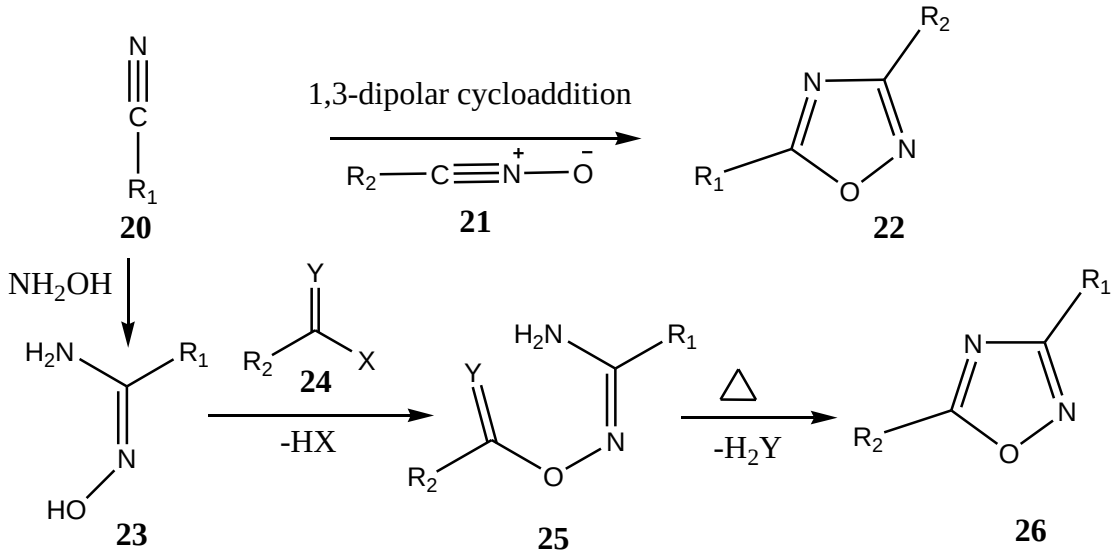



**Fig. 1.11**

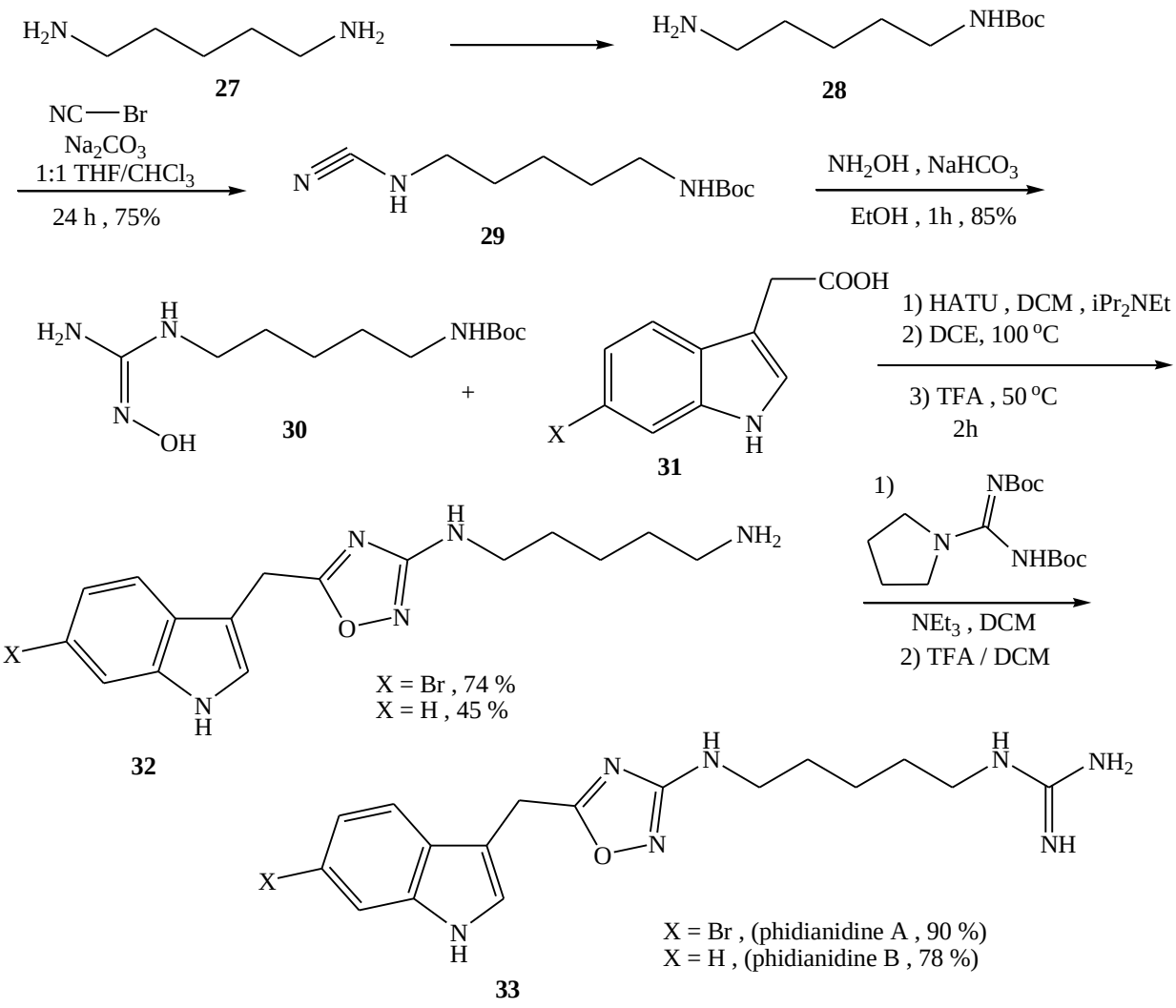
### 1.1.2. Synthesis of 1,2,4-oxadiazoles

1,2,4-Oxadiazoles are easy to make using 1,3-dipolar cycloaddition reactions between nitriles **20** and nitrile oxides **21**, or from the reactions of amidoximes **23** (made from nitrile reaction with hydroxylamine) with a carboxylic acid derivative **24**[44-46].



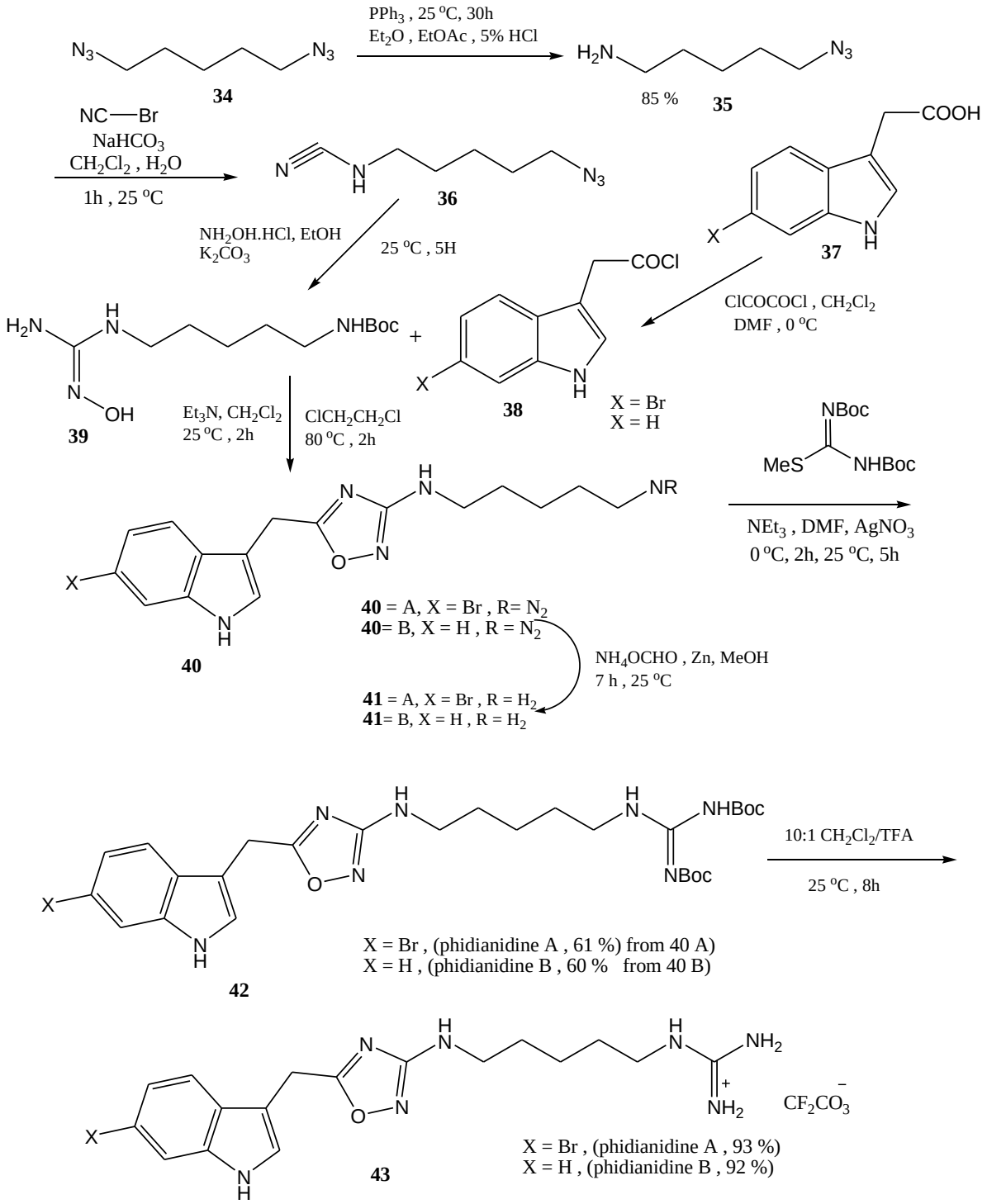

**Scheme 1.1**

The synthesis of phidianidines A and B **33**, the first 1,2,4-oxadiazole containing natural product (from the marine opistho branch mollusc, Phidiana militaris), has been reported recently as an example of the reaction of nitrile derived amidoxime with a carboxylic acid derivative. Lindsley and co-workers[47] (scheme 1.2) reported the synthesis of phidianidine A and B, starting from 1,5-diaminopentane, converting it to the amidoxime and then reacting with indole acetic acid to give phidianidine A and B in 39.9 % and 21 % respectively.




**Scheme 1.2**

Snider *et al.* (scheme 1.3) have used a similar strategy to synthesize phidianidine A and B in 19 % overall yield. They reacted a substituted indole-3-acetyl chloride with *N*-5-azidopentyl-*N*'-hydroxyguanidine (obtained from 1,5-diazidopentane) to produce 3-(5-azidopentylamino)-5-((indole-3-yl)-methyl)-1,2,4-oxadiazole. The azide was reduced with zinc and ammonium formate to afford the corresponding amine which was elaborated to guanidine, completing the synthesis of phidianidine A and B[48].




**Scheme 1.3**

1,2,4-Oxadiazoles substituted with a heteroatom will form part of the discussion of this thesis. A brief survey of such systems is given here.

### 1.1.2.1. Keto- and amino-1,2,4-oxadiazoles

3-Keto-1,2,4-oxadiazoles **44** have been synthesized by using amidoxime route. The carbonyl group was formed by liberating TBS-protected alcohol followed by oxidation with Dess-Martin periodinane[49]. An alternative method involves the synthesis of 3-acyl-1,2,4-oxadiazoles as a result of a reaction of nitrile with methyl ketone in the presence of iron (III) nitrate, a reaction similar to the Mukaiyama-Hoshino method[50]. The mechanism involves the α-nitration of ketone and loss of water to form nitrile oxide *in situ* which cyclises with the nitrile to produce the product[50]. An example of a 5-keto-1,2,4-oxadiazole **45** has been recently reported as an anti-inflammatory agent[18].

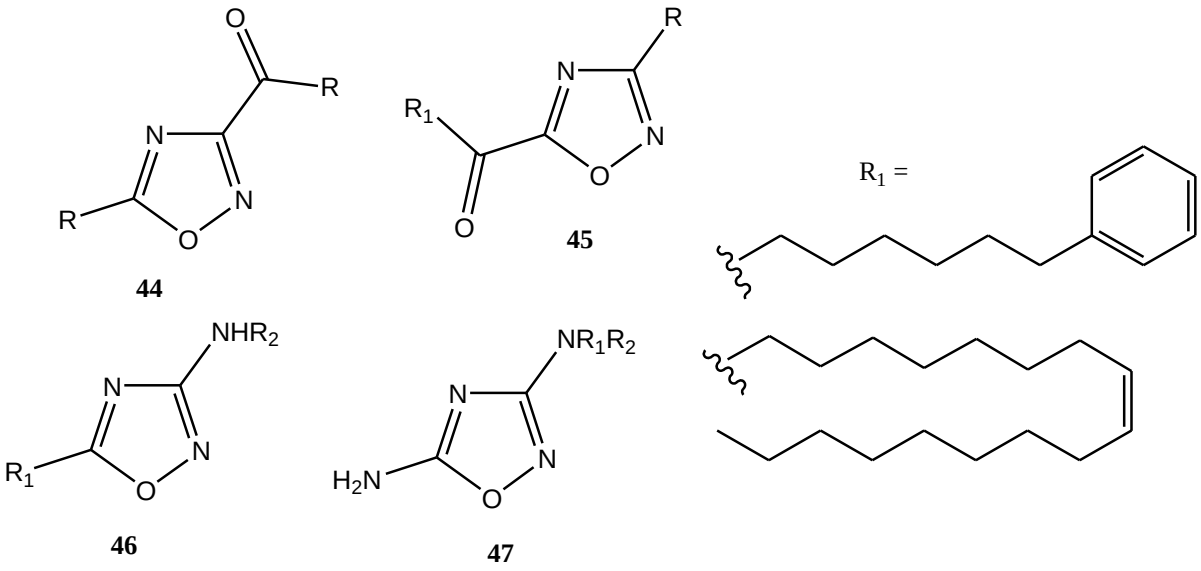
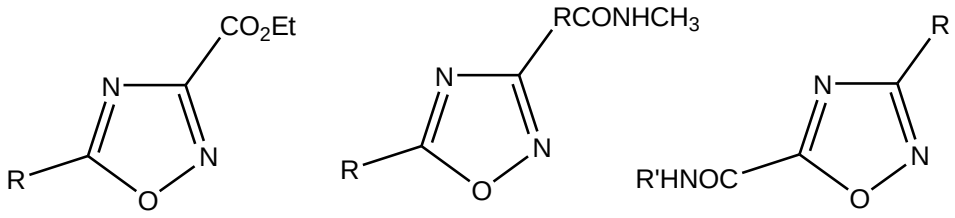



**Fig. 1.12**

Several methods have been used for the synthesis of amino-1,2,4-oxadiazoles. Aromatic nucleophilic substitution ($S_NAr$) of 5-trichloromethyl-1,2,4-oxadiazole[51,52] and cyclization of amidoximes with carbodiimides[53] are considered as the most convenient methods. Photochemical reaction of 3-acylamino-1,2,5-oxadiazole[54] in the presence of amines also produces 3-amino-1,2,4-oxadiazoles **46**, whereas, 3,5-diamino derivatives **47** have been reported as a result of reaction of 3-cyanoisothioureas with hydroxylamine[55].

### 1.1.2.2. Ethoxycarbonyl and carbamoyl-1,2,4-oxadiazoles

Synthesis of 3-ethoxycarbonyl derivatives **48** has been done by reacting amidoxime with anhydrides[56] or *N*-acylamidoxime[57]. 3-Carbamoyl derivatives **49** are prepared from anhydride reaction with amidoximes derived from nitroisoxazolone[58]. Reaction of amidoxime with ethyl oxalyl chloride produces 5-ethoxycarbonyl-1,2,4-oxadiazoles[59] which can be converted to 5-carbamoyl-1,2,4-oxadiazoles **50** after aminolysis[59]. These are important compounds for further modifications of side chains.

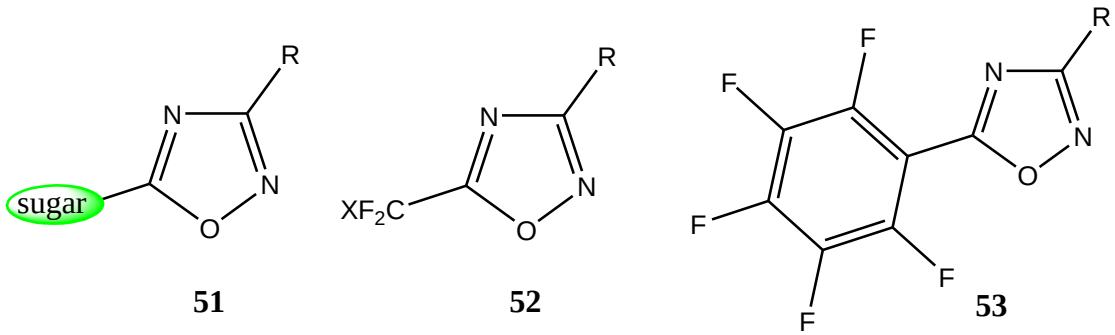



**48** **49** **50**

**Fig. 1.13**

### 1.1.2.3. Sugar linked and fluorinated 1,2,4-oxadiazoles

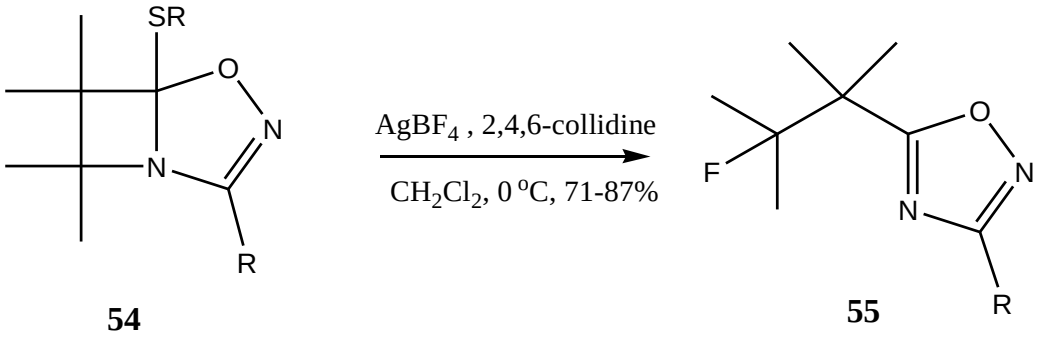
The linking of a carbohydrate moiety to bioactive oxadiazoles can increase their pharmacological properties e.g. increase their water solubility. Sugar cyanohydrins, being easily accessible, are used as 1,2,4-oxadiazole synthons to do cycloaddition with nitrile oxides to produce 5-glycosyl derivatives **51** [60], or to produce amidoxime which produce 3-glycosyl-1,2,4-oxadiazoles[33]. Sugar linked 1,2,4-oxadiazoles have also been synthesized from azidoglycosides or azidophenyl-1,2,4-oxadiazles through a 1,2,3-triazole ‘’click’’ spacer[61,62].




**51** **52** **53**

**Fig. 1.14**

Fluorinated azoles have shown their importance in pharmaceutical industry as well as in material sciences. There have been several reports on the synthesis of fluorinated 1,2,4-oxadiazoles[63]. Fluorinated 1,2,4-oxadiazoles **52** have been used as reagents in the presence of sodium dithionite, to introduce the difluoromethylene group into organic compounds[64]. The attachment of fluorinated moieties to macromolecules[65,66] and polymers[67,68], has been performed by using 5-pentafluorophenyl-1,2,4-oxadiazoles **53** as fluorinated oxadiazole arylating reagent (FOXARs)[69]. Hemming and co-workers have reported the synthesis of 5-(2'-fluoro-2,3-dimethylbutan-3-yl) substituted 1,2,4-oxadiazoles **55** through fluorodesulfurization of 5-ethylthio-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-enes **54** with silver tetrafluoroborate[70].

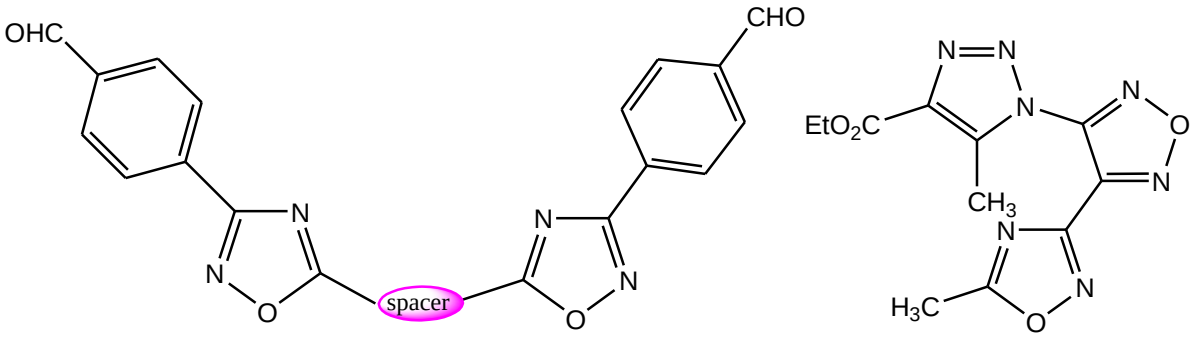



**54** **55**

**Scheme 1.4**

### 1.1.2.4. Heterocyclic linked 1,2,4-oxadiazoles

A heterocycle can be linked to a 1,2,4-oxadiazole system to increase its physiochemical or biological properties. Many such systems have been reported in the literature[1], for example, 1,2,4-oxadiazole ring has been introduced in 3-[(1,2,4-oxadiazole-3-yl)-methyl]-3,4-dihydropyrimidine-2(1H)-ones as a bioisostere of esters and amides. These compounds have been synthesized by ionic liquid-phase organic synthesis (IoLiPOS)[71]. Synthesis of *bis* (1,2,4-oxadiazoles) has been reported including one involving several spaced *bis*[(1,2,4-oxadiazole)-benzaldehyde] building blocks **56** [72]and another involving *N*, *N*'-protected bis(5-aminoalkyl-1,2,4-oxadiazol-3-yl)methane[73]. Similarly the *tris* (heterocycle) **57** has been synthesized consisting of 1,2,3-triazole, 1,2,4- and 1,2,5-oxadiazole rings[74]. Such poly (heterocycles) can be useful as metal ligands in metal organic frameworks.

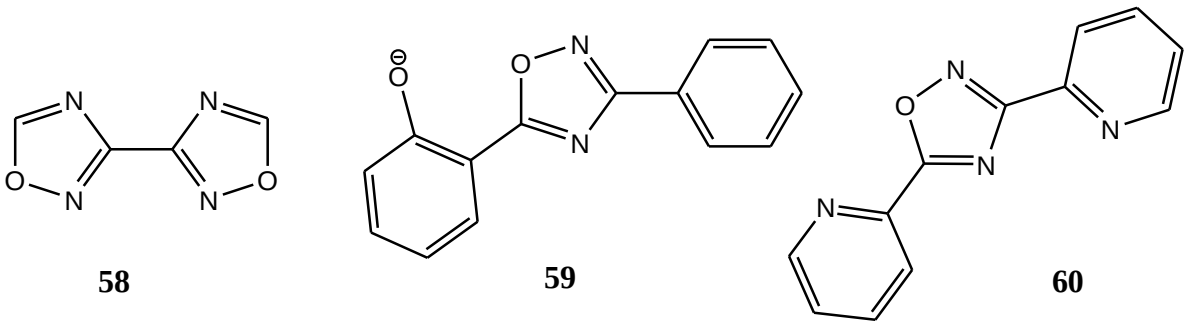



**56** **57**

**Fig. 1.15**

### 1.1.2.5. Metal complexes of 1,2,4-oxadiazoles

Coordination complexes containing 1,2,4-oxadiazole systems have been reported[46], particularly complexes with the oxadiazole acting as a monodentate ligand with Cu(II), Co(II), Zn(II), pd(II), Pt(II)[75]. Some Pd and Pt complexes containing 1,2,4-oxadiazoles have been synthesized by 1,3-dipolar cycloaddition of nitrile oxide and nitrile metal complexes[76]. 1,2,4-Oxadiazol-3-yl-bipyridine chelate iron and copper and show similar features to terpyridyl complexes[77]. 3,3'-Bis[1,2,4-oxadiazol] **58** synthesized by Moussebois and Eloy[78] has been identified as a ligand for palladium and silver complexes[42]. The Cu (II) complex of 5-(2'-oxyphenyl)-3-phenyl-1,2,4-oxadiazole **59** has been observed as fluorescent at room temperature[79]. 3,5-*Bis*(2'-pyridyl)-1,2,4-oxadiazole **60** complexes of copper, nickel and zinc have been synthesized and evaluated for their DNA-binding interactions[80].

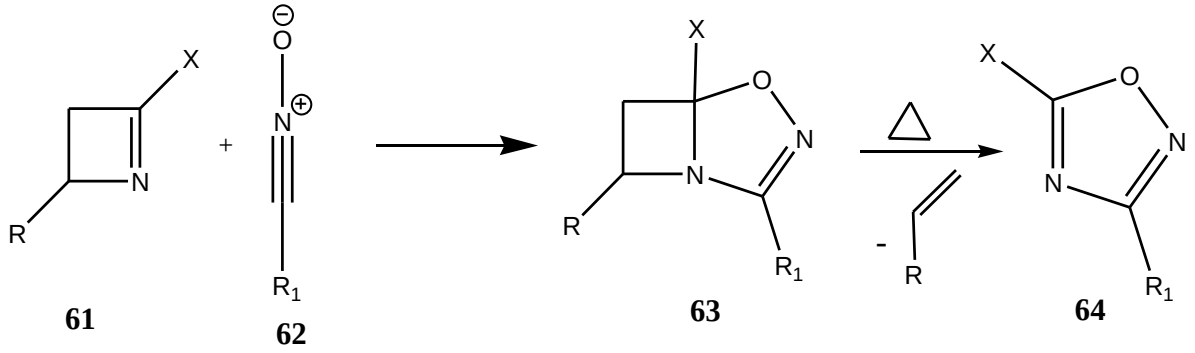



**58** **59** **60**

**Fig. 1.16**

In our strategy, 1-azetines were synthesized and reacted with different nitrile oxides to afford a series of oxadiazabicyclo[3.2.0]-hept-2-enes. Heating these bicyclic adducts in toluene

resulted in an overall [2+2]-cycloreversion to produce 5-alkylthio-3-aryl-1,2,4-oxadiazoles. This work was a continuation of the earlier fluoro-work shown above where compound **54** gives compound **55**.




**61** **62** **63** **64**

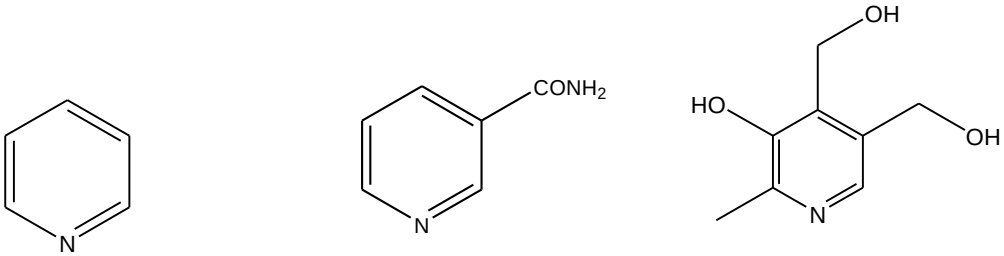
**Scheme 1.5**

## 1.2 Pyridines

Pyridines **65** are a class of heterocyclic compounds which are similar to benzene in structure with one CH group replaced by nitrogen atom. Pyridine has been found important in the understanding of the chemistry of many biological systems. It is useful in the catalysis of both chemical and biological systems. In living organisms many enzymes contain the pyridine nucleotide (NADP) that is involved in many oxidation-reduction processes[81]. A brief and selective survey of pyridines is given below.

### 1.2.1. Biological importance of pyridines

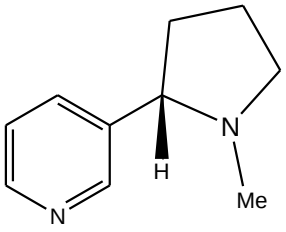
Pyridine's importance in biological systems is shown by important vitamins such as niacin **66** and pyridoxine **67** (which is involved in, for example, the production of red blood cells) and also in highly toxic alkaloids such as nicotine **68**[82] .



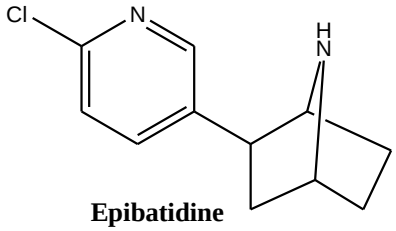

**Pyridine** **65** **Niacin** **66** **Pyridoxine** **67**

**Fig. 1.17**

A well known naturally occurring pyridine is epibatidine **69**, an alkaloid, which was originally found in the skin of a neotropical poisonous frog, *Epipedobates tricolor*, found in Ecuador.



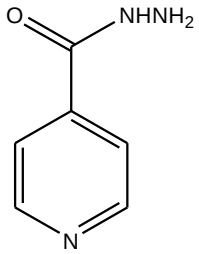

**Nicotine**
**68**



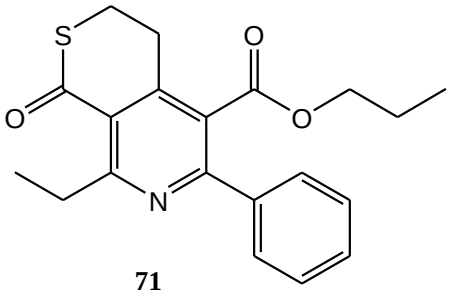

**Epibatidine**
**69**

**Fig. 1.18**

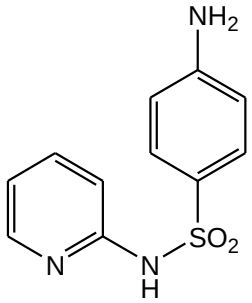
In the pharmaceutical industry, pyridines are involved in the synthesis of over 7000 drugs[83-86]. Some of them are shown below.



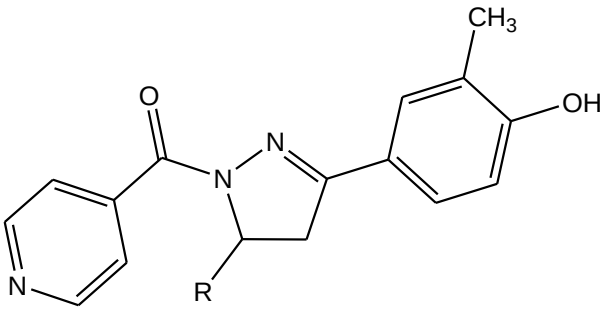

**Isoniazide**
**(Antituberculosis)**
**70**




**71**
**A3 adenosine receptor antagonist**
**(Antiinflammatory, Antiasthmatic)**



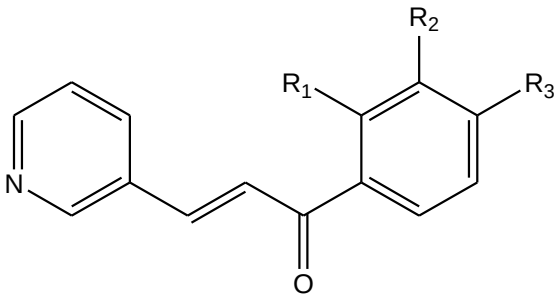

**72**
**Sulphapridine**
**(Antibacterial)**




**Antimicrobial and anti-HIV agent**

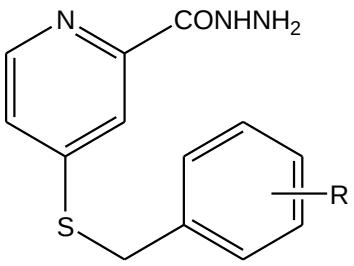
**73**

**Fig. 1.19**




**Antibacterial and antifungal**

**74**

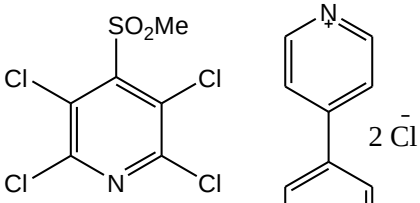



**Antituberculosis**

**75**

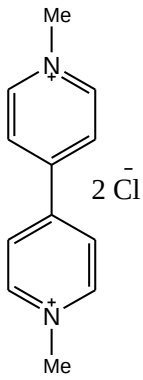
**Fig. 1.20**

Pyridines are also found in many agrochemicals,[83,87] some of which are shown below.



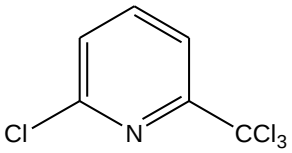

**Davicil (fungicide)**

**76**



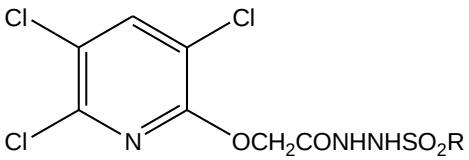

**Paraquat (Herbicide)**

**77**




**Nitrapyrin (Bactericide)**

**78**




**Herbicide**

**79**

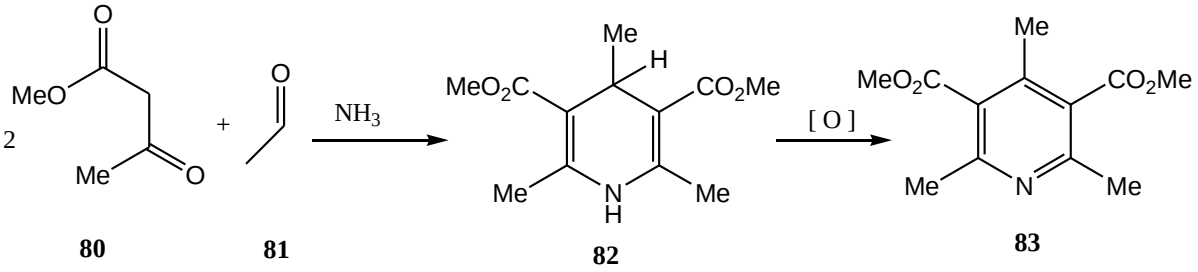
**Fig. 1.21**

## 1.2.2. Synthesis of pyridines

Since the discovery of pyridines, several methods have been used for its synthesis. The more commonly used methods involve the condensation of amine and carbonyl compounds. Such methods are characterized by the number of atoms in each fragment contributing to the heterocyclic ring. Ammonia serves as a source of nitrogen in [5+1] condensation with 1,5-dicarbonyl compounds[88] followed by oxidation for aromatization of the ring. It is also involved in the [2+2+1+1] Hantzsch synthesis[89,90] of pyridines, a commonly used method first described by Hantzsch in 1882[89]. In this reaction two equivalents of a β-keto ester are reacted with an aldehyde in the presence of ammonia to form a dihydropyridine, and after

oxidation a pyridine is formed. Alkyl and vinyl amines are used in [3+3] condensation with 1,3-dicarbonyl derivatives[91] to synthesize pyridines.

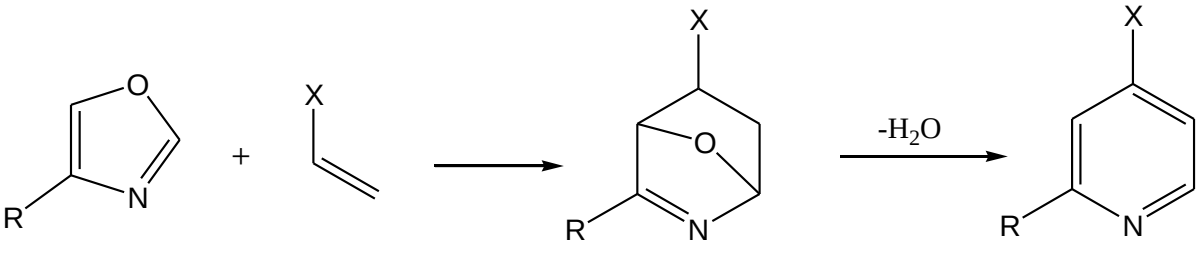
The Hantzsch synthesis is important for the synthesis of fully substituted pyridines, but is limited to carboxyl substituents at the 3- and 5-positions and often requires an aryl substituent at the 4th position[92]. Despite its limitations the Hantzsch synthesis has been of huge interest for over a century, not least because of its use in the synthesis of many dihydropyridine anti-hypertensives.




**80** **81** **82** **83**

**Scheme 1.6**

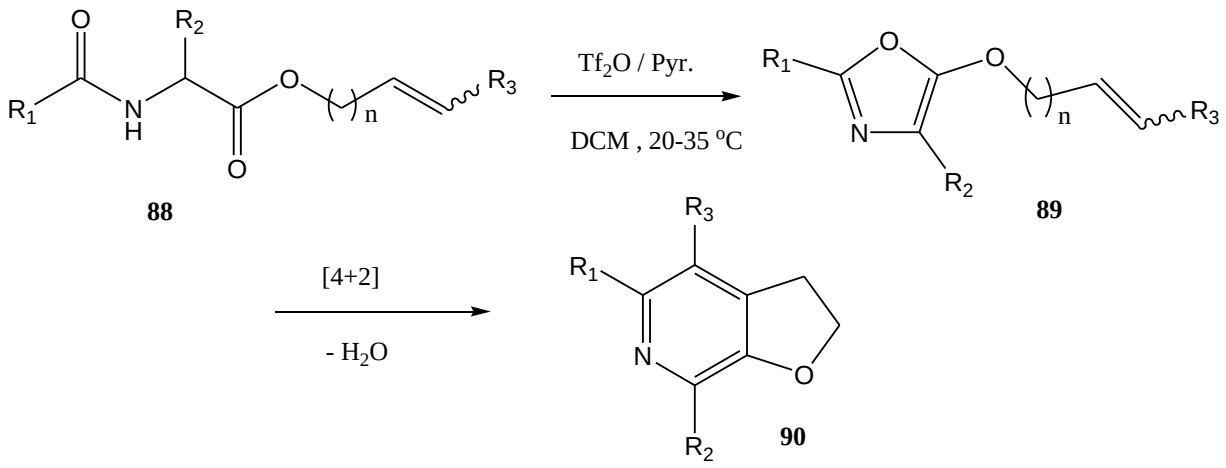
In 1965[93], Kondrat'eva and Huan described a method involving addition of a dienophile to oxazole , where subsequent extrusion of the oxygen atom results in the formation of a pyridine.



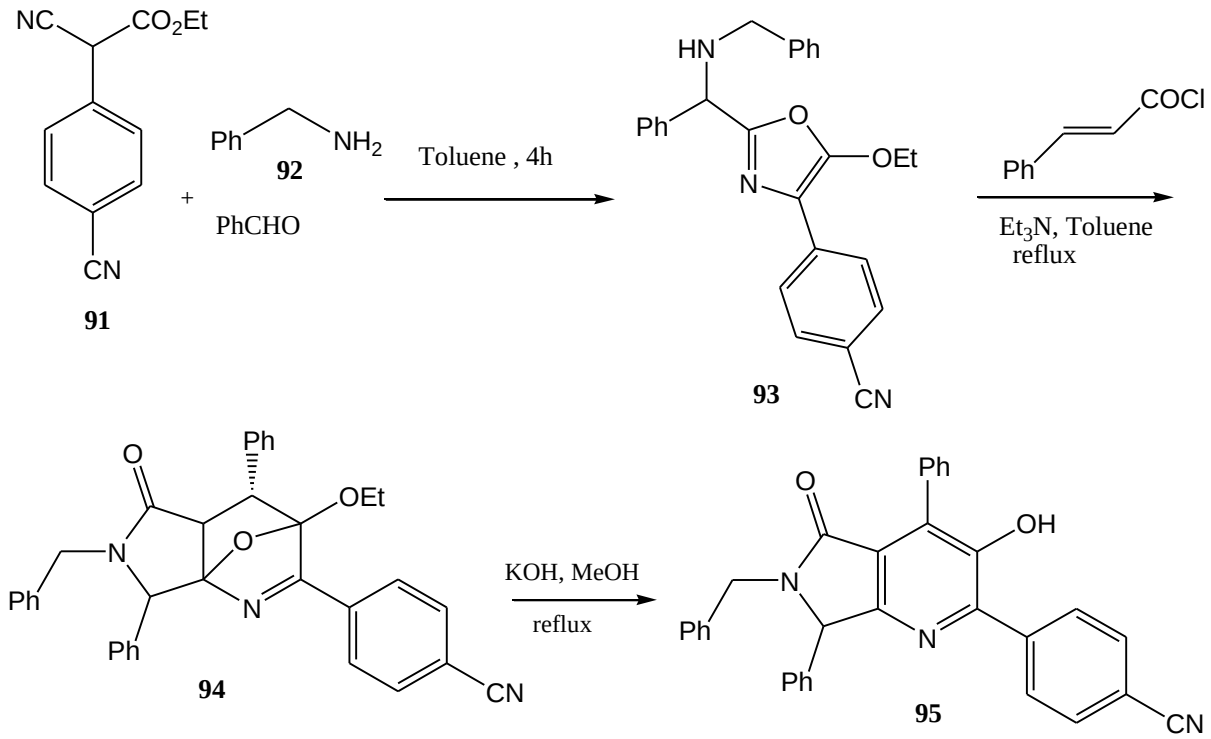

**84** **85** **86** **87**

**Scheme 1.7**

As will be seen later, this is similar to the method developed in the work described in this thesis. This method has been reported regularly for the synthesis of pyridines and some recently reported examples are given below [94,95].




**Scheme 1.8**




**Scheme 1.9**

## 1.2.2.1 Recent developments in pyridine synthesis

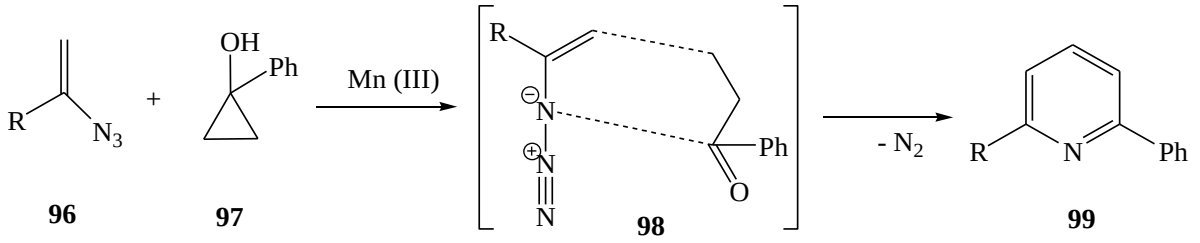
Pyridine synthesis continues to be of huge interest and in recent years, various new methods[96] including new cycloaddition approaches[96,97] have been reported. A short review of some

recent methods appears below. Pyridine synthesis was reviewed in 2010, so the below reports synthesis methods since then.

### 1.2.2.1.1 Pyridine synthesis via cycloaddition

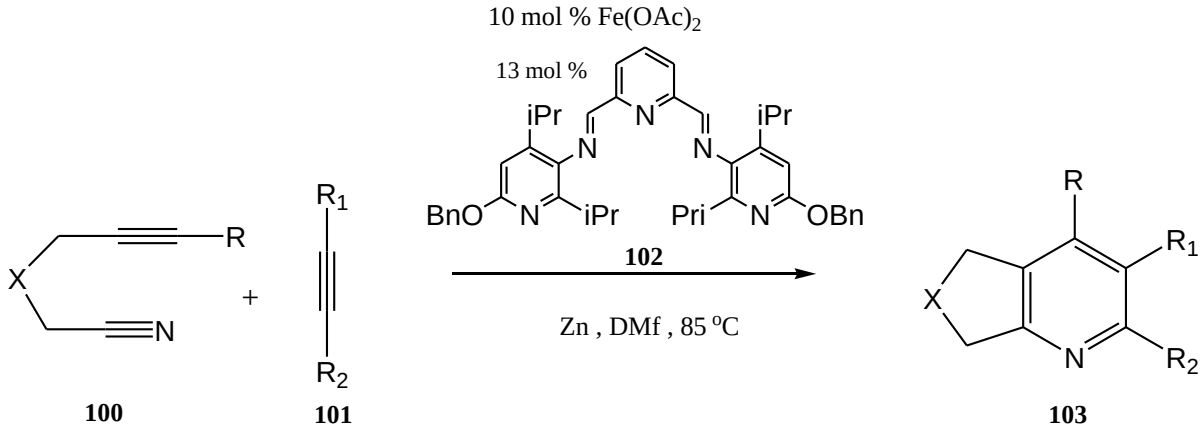
Historically, cycloaddition is one of the most widely used method for the pyridine synthesis and there are various established cycloaddition methodologies[96]. However, some new cycloaddition approaches have been reported which will be discussed here.

Vinyl azides have been used as a three atom unit including one nitrogen to synthesize pyridines, by reacting it with monocyclic propanols. The reaction starts with oxidation of cyclopropanol to generate β-carbonyl radical in the presence of Mn (III). The radical addition of β-carbonyl to vinyl azide forms an iminyl radical which cyclises with the intramolecular carbonyl group to afford the pyridine[98].



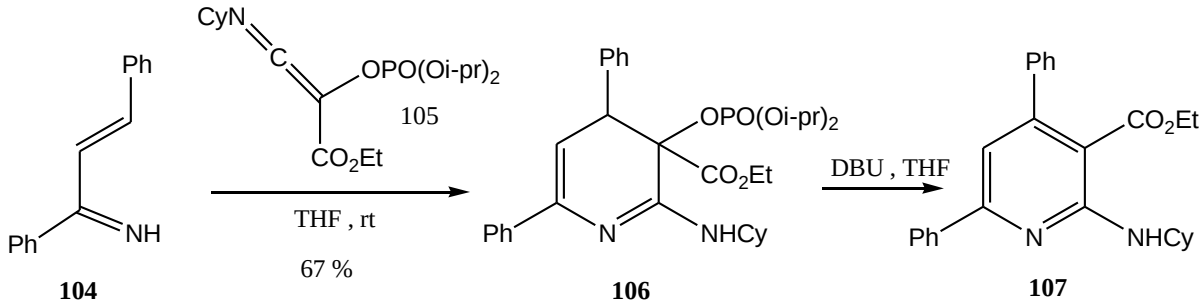

**Scheme 1.10**

A number of substituted pyridines have been synthesized by using iron (II) acetate and pyridyl bisimines as catalysts for the [2+2+2] cycloaddition of alkynes and alkynylnitriles[99].



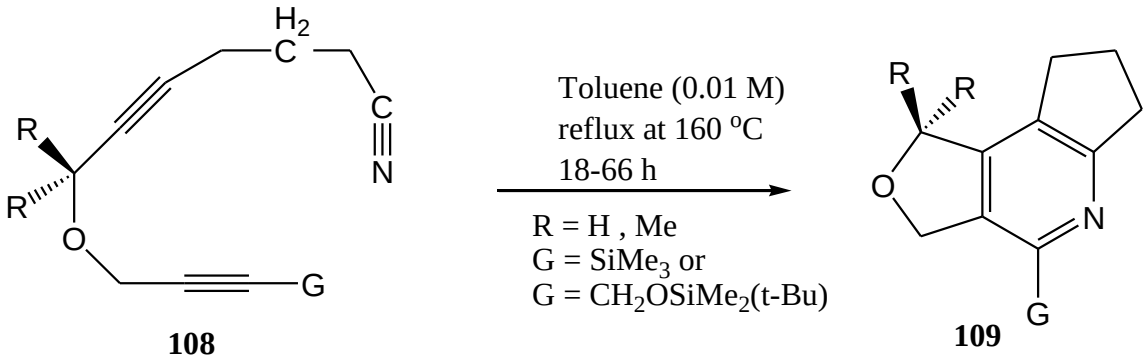

**Scheme 1.11**

Coffinier *et al.* have reported pyridine syntheses by coupling two multicomponent processes involving 1-azadienes and ketenimines. 1-Azadienes were formed *in situ* in a one-pot reaction of phosphonates, nitriles and aldehydes and reacted with ketenimines prepared from oxalic acid monoethyl ester chloride which was in turn prepared from the corresponding isocyanide and trialkylphosphite. The reaction produces a dihydropyridine which is converted to pyridine by phosphate elimination under basic treatment with DBU[100].



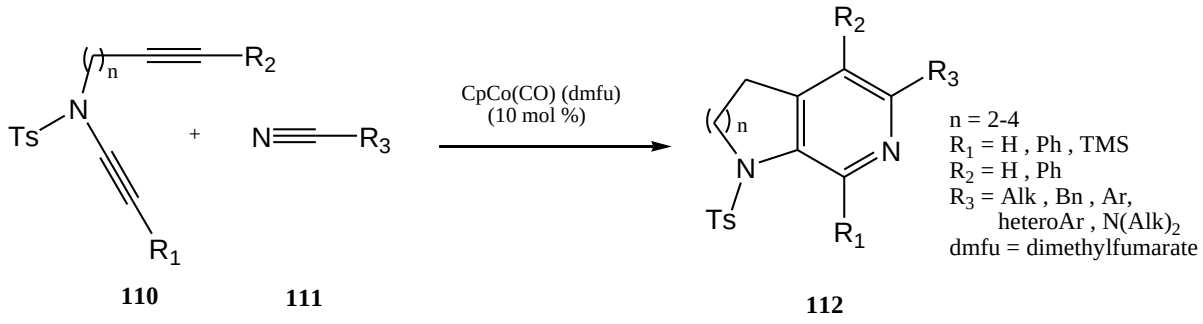

**Scheme 1.12**

Hapke and co-workers have reported the synthesis of pyridines through [2+2+2] cycloaddition reactions of cyanodiynes[101]. A similar startegy was used by Danheiser and co-workers for a polycyclic pyridine synthesis via metal free [2+2+2] cycloaddition that proceeds through a pericyclic cascade mechanism involving unactivated cyano groups as enophile and dienophiles[102].




**Scheme 1.13**

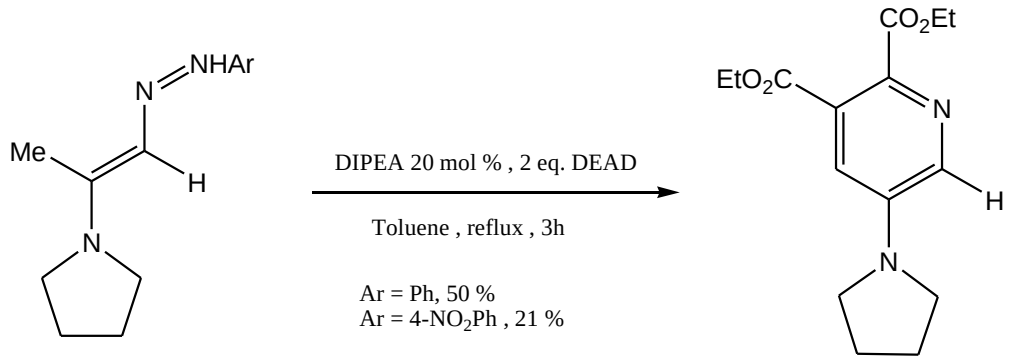
Regioselective bicyclic 3- and 4-aminopyridines have been synthesized through cobalt catalyzed [2+2+2] cycloaddition between yn-ynamides and nitriles in excellent yields, with high regioselectivity in the products[103], as shown in scheme 1.14.




**110** **111** **112**

**Scheme 1.14**

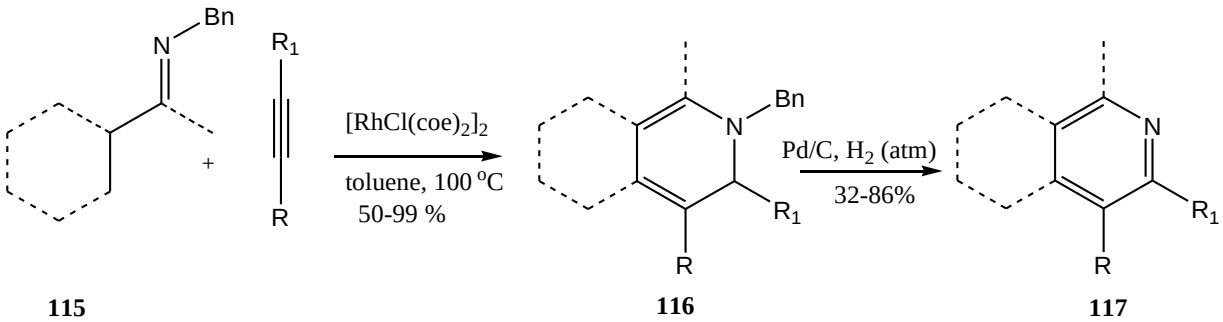
Cycloaddition of azoenamines with acetylendicarboxylates has resulted in the synthesis of pyridines. Azoenamines are produced from reaction of α-ketohydrazones with secondary amines[104] in the presence of diethyl acetylenedicarboxylate.




**113** **114**

**Scheme 1.15**

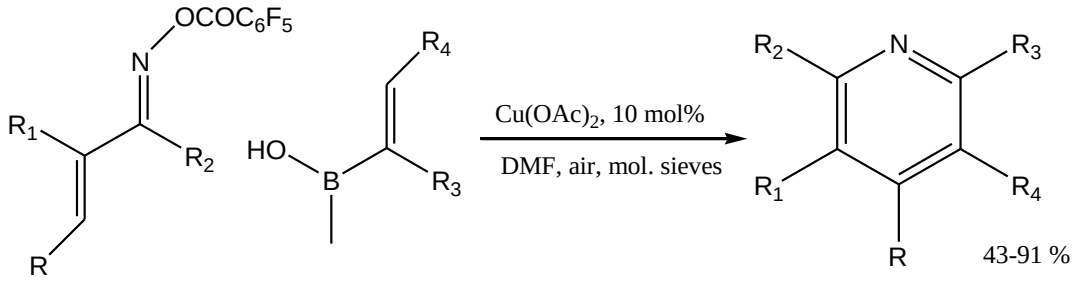
Ellman has used rhodium as a catalyst for C-H activation during a one-pot alkenylation/electrocyclization/aromatization process to synthesize substituted pyridines from alkynes and α,β-unsaturated imines[105].




**115** **116** **117**

**Scheme 1.16**

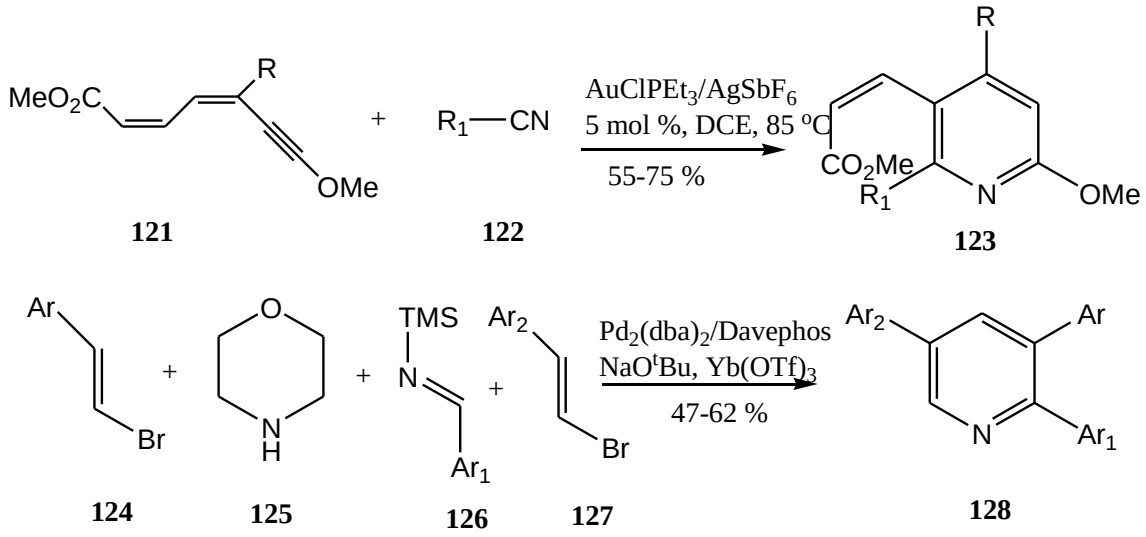
Liebeskind has adopted an approach involving the copper catalyzed reaction of alkenylboronic acids and α,β-unsaturated oxime O-carboxylates for the synthesis of substituted pyridines[106].




**118** **119** **120**

**Scheme 1.17**

Barluenga and his co-workers [107,108] have presented two different approaches for the synthesis of substituted pyridines. The first involves the gold catalyzed intermolecular hetero-dehydro-Diels-Alder reaction between dienynes and nitriles, which leads to the regioselective formation of tetrasubstituted pyridines. In the second approach they used Pd as a catalyst for a multicomponent, one-pot synthesis of trisubstituted pyridines, and this occurs via cross-coupling/cross-coupling/cycloaddition and proceeds through 2-azadiene intermediates.



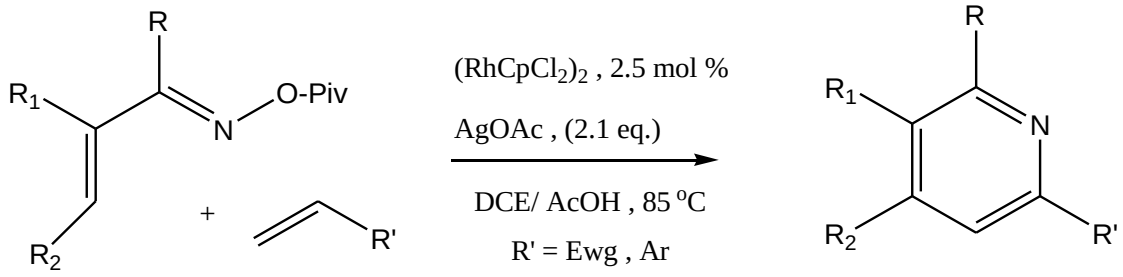

**121** **122** **123**

**124** **125** **126** **127** **128**

**Scheme 1.18**

## 1.2.2.1.2 Other methods for pyridine synthesis

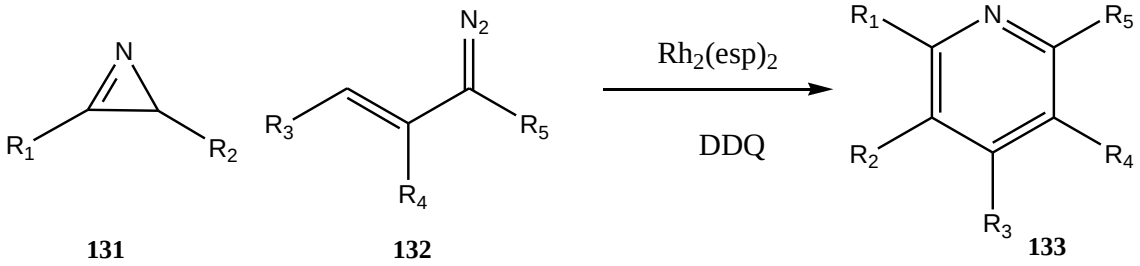
Rovis and co-workers have recently reported a Rh (III) catalyzed regioselective synthesis of pyridines by coupling α,β-unsaturated O-pivaloyl oximes to alkenes. The reaction involves reversible C-H activation followed by alkene insertion and in the next step C-N bond formation/ N-O bond cleavage completes the pyridine formation[109].




**129** **130**

**Scheme 1.19**

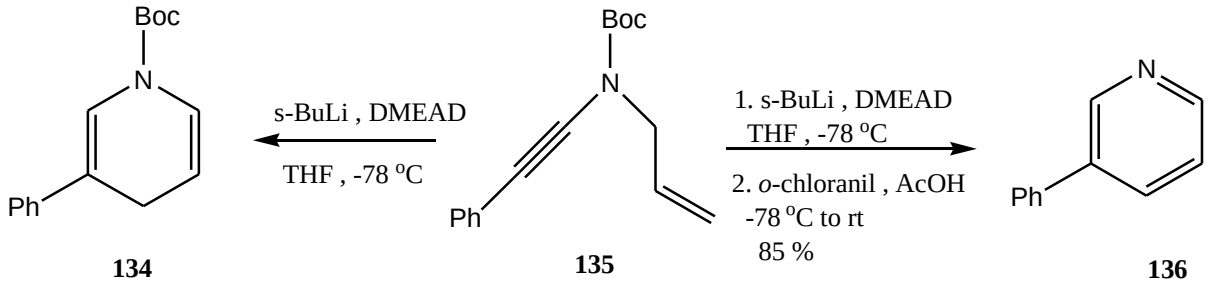
Park has used the reaction of 2H-azirines with vinyl diaza compounds and shown that this yields pyridines in the presence of a Rh catalyst. The reaction is believed to proceed through a carbenoid intermediate and DDQ oxidation of a non-isolated dihydropyridine[110].




**131** **132** **133**

**Scheme 1.20**

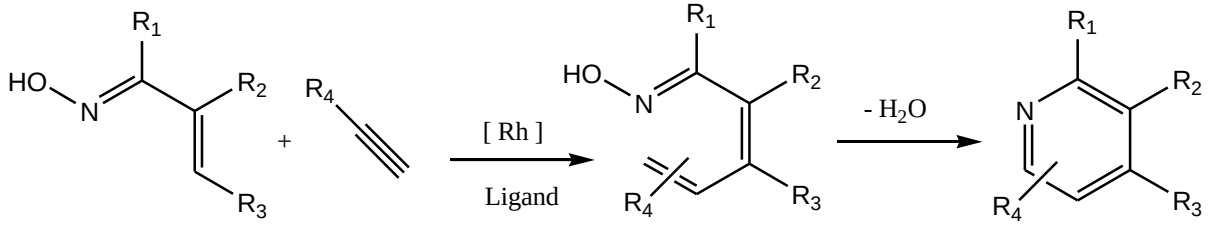
Synthesis of 1,4-dihydropyridines and pyridines through a general method that includes lithiation/isomerisation/intramolecular carbolithiation of readily available *N*-allyl ynamides has been developed[111].




**134** **135** **136**

**Scheme 1.21**

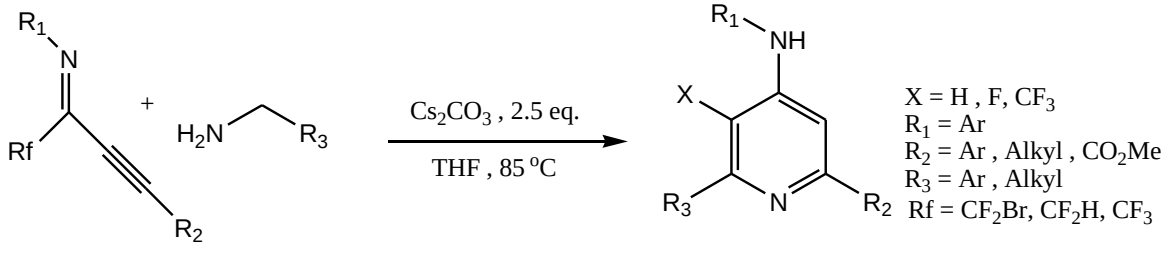
Pyridines can also be synthesized by one step Rh catalyzed C-H bond functionalization of α,β-unsaturated ketoximes and terminal alkynes. This regioselective synthesis of pyridines proceeds through the use of triisopropyl phosphate as a ligand that suppresses the undesired dimerization of terminal alkynes to enynes[112].




**137** **138** **139**

**Scheme 1.22**

Polysubstituted 3-H, 3-F and 3-trifluoromethyl pyridines **142** (X = H, F or $CF_3$) have been synthesized on the basis of C-F bond breaking of anionically activated fluoroalkyl groups. This is a high yielding process for the synthesis of 2,6-disubstituted 4-aminopyridines[113].

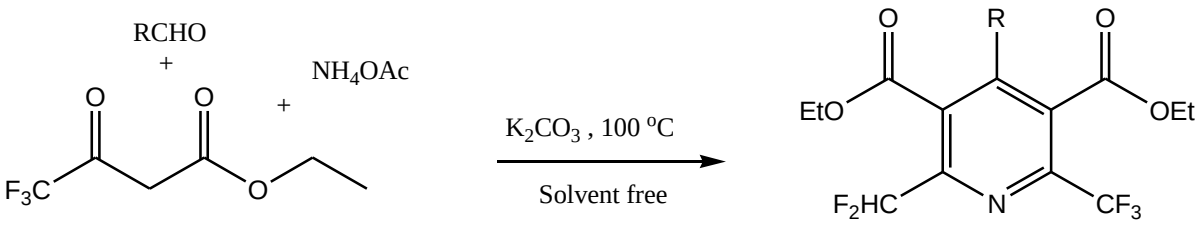



**140** **141** **142**

**Scheme 1.23**

Three component reaction of trifluoroacetoacetate, aldehydes and ammonium acetate results in the synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates in the

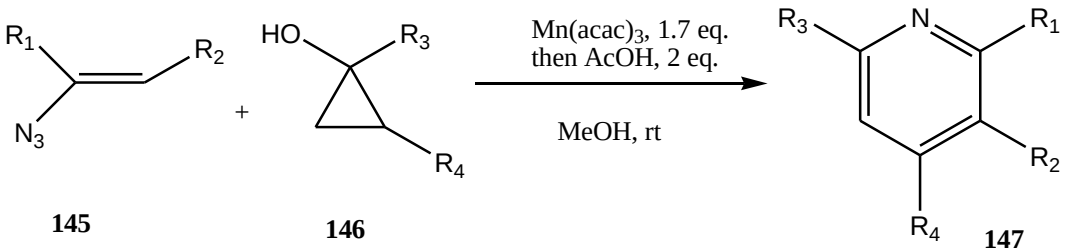
presence of potassium carbonate under solvent free conditions. The reaction proceeds via Hantzsch reaction/dehydration/dehydrofluorination in a one-pot reaction[114].




**143** **144**

**Scheme 1.24**

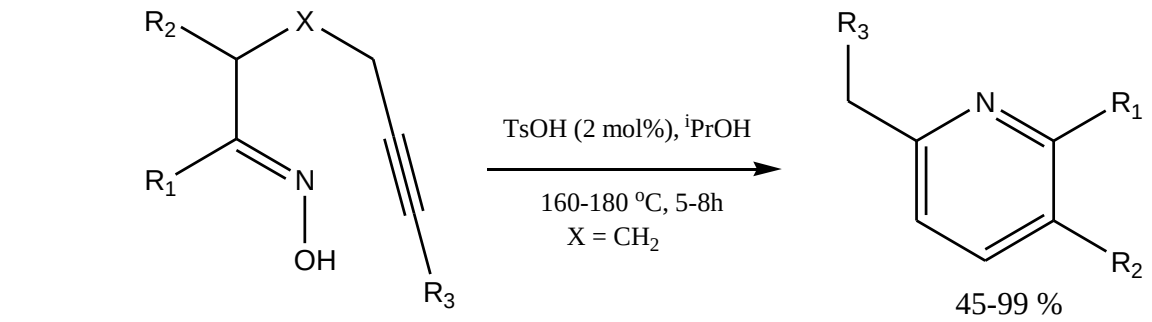
Chiba and Wang have developed a Mn (III) mediated reaction of cyclopropanols and vinyl azides to synthesize tetrahydropyridines which undergo dehydration and oxidation in the presence of excess Mn (III), AcOH and oxygen to produce pyridines[115].




**145** **146** **147**

**Scheme 1.25**

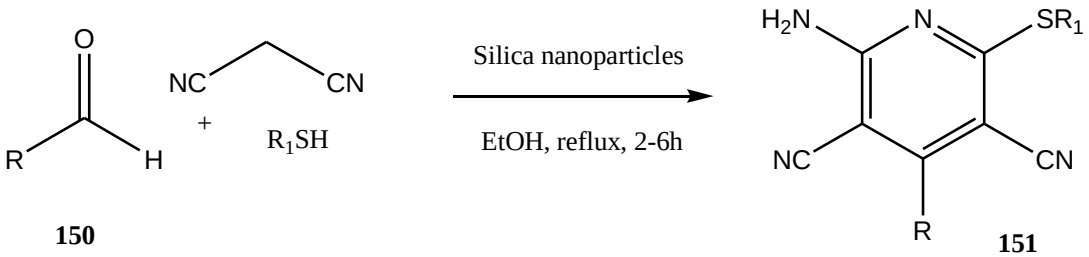
Beauchemin and co-workers[116] successfully synthesized pyridines from an intramolecular Cope-type hydroamination reaction starting with alkynyl oximes and proceeding through isomerisation and aromatization.




**148** **149**

**Scheme 1.26**

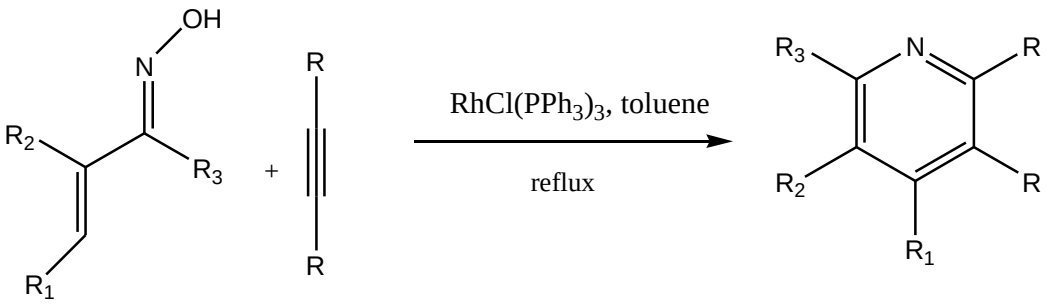
Banerjee and Sereda adopted a silica catalysed approach for the the synthesis of pyridines from aldehydes, malononitrile and thiols under mild and near neutral conditions[117].




**150** **151**

**Scheme 1.27**

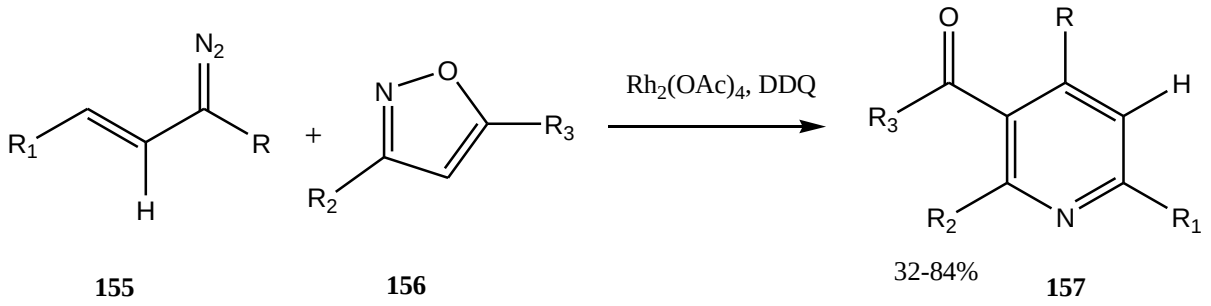
Cheng has reported the synthesis of fully substituted pyridines with the help of α,β-ketoximes and alkynes, where C-H activation of α,β-ketoximes occurred with rhodium catalyzed chelation[118].




**152** **153** **154**

**Scheme 1.28**

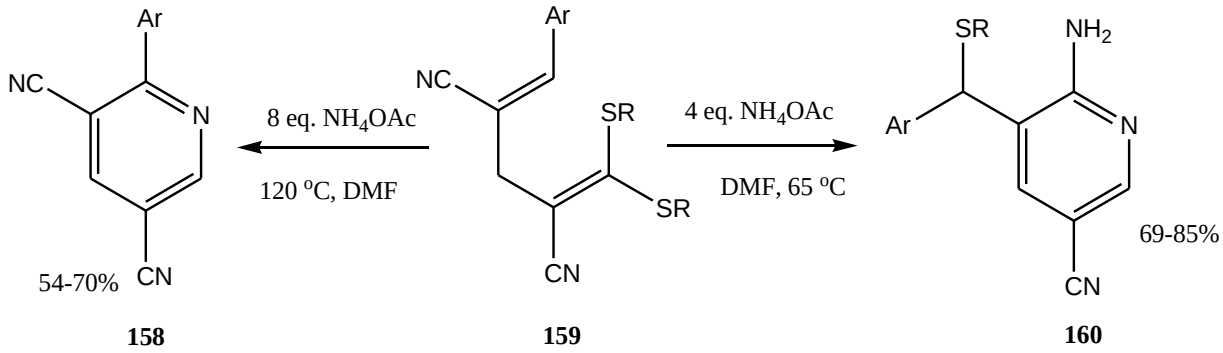
Davies and co-workers have reported a one pot synthesis of highly functionalised pyridines which involves the Rh-catalyzed reaction of isoxazoles with diazoacetates that proceeds through carbenoid induced ring expansion followed by a rearrangement, oxidation sequence[119].




**155** **156** **157**

**Scheme 1.29**

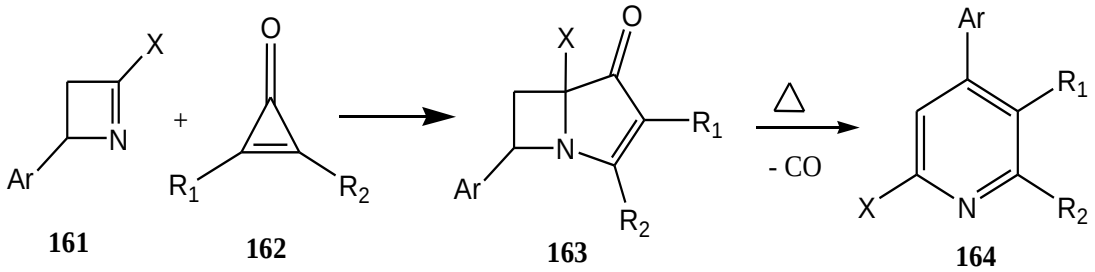
Zhang, Liu *et al.* have used a novel temperature-controlled methodology for the synthesis of substituted pyridines, where (5C+1N) annulations of 1,1-bisalkylthio-1,4-pentanedienes with ammonium acetate results in two different pyridine products at two different temperatures. Reaction at 120 $^0$C gave 3,5-dinitrile pyridines while the reaction at 65 $^0$C gave 2-amino-3-alkylthio-pyridines[120].




**158** **159** **160**

**Scheme 1.30**

In our strategy, azabicyclo[3.2.0]hept-2-en-4-ones were synthesized from the reaction between 4-aryl-1-azetines and readily available cyclopropenones, where the cyclopropenones behave as all carbon 1,3-dipole equivalents. Heating the azabicyclic adduct in toluene produced pyridines through a proposed azacyclopentadienone intermediate generated as a result of [2+2]-cycloreversion. Diels-Alder reaction between the proposed intermediate azacyclopentadienone and styrene followed by chelotropic extrusion of carbon monoxide and loss of hydrogen gives pyridines.




**161** **162** **163** **164**

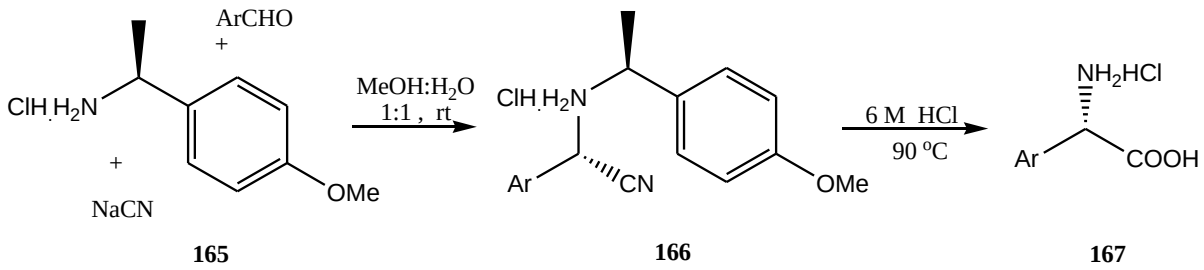
**Scheme 1.31**

## 1.3 Multicomponent reactions of aryl aldehydes

Multicomponent reactions are a class of domino reactions involving at least three substrates to form a product that contains a portion of each component. These reactions achieve multibond formation in a one-pot reaction and form complex products from simple starting materials. These multicomponent reactions are highly flexible, convergent, chemoselective and atom efficient as they avoid protecting groups and isolation of intermediates. Multicomponent reactions were first reported in the 19$^{th}$ century by Strecker, Hantzsch and Biginelli but it is after the more recent work of Ugi and co-workers that this strategy evolved[121-123].

### 1.3.1. Multicomponent Strecker reactions

The Strecker reaction is a three component coupling between a carbonyl derivative, amine and a cyanide source to produce the corresponding α-aminonitriles. It was first reported in 1850[124] and is one of the most commonly used methods for the synthesis of α-aminonitriles that can be hydrolysed to α-amino acids[125-129]. The reaction proceeds through an initial formation of imine by the condensation of carbonyl and amine components followed by the addition of cyanide to the imine intermediate to form the product. A recent example of a Strecker reaction has been reported by James and co-workers[130] for the synthesis of enantiopure α-arylglycines through an asymmetric three component reaction of arylaldehydes, sodium cyanide in solution and (*S*)-1-(4-methoxyphenyl)-ethylamine as the easily removed chiral auxiliary.




**165** **166** **167**

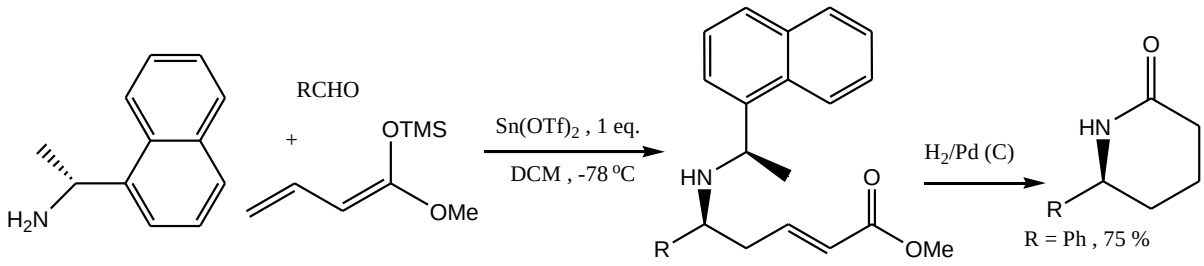
**Scheme 1.32**

### 1.3.2. Multicomponent Hantzsch reaction

The Hantzsch reaction was first reported in 1882[89] for the synthesis of 1,4-dihydropyridines from the reaction of enamine, aldehyde and a 1,3-dicarbonyl compound. A recent example of Hantzsch milticomponent reaction for pyridine synthesis has been described in the previous section of this chapter.

### 1.3.3. Multicomponent Mannich reaction

The classic Mannich reaction involves ammonia (or a primary or secondary amine), a nonenolizable aldehyde or ketone and an enolizable carbonyl compound to form β-amino-carbonyl products[131-133]. It was first reported in 1912[134] and since then, use of various chiral starting materials for this asymmetric multicomponent reaction have been reported including enantioselective catalytic Mannich reactions[135]. Yang *et al*. have recently reported a stereoselective approach to chiral 6-alkylated 2-piperidinones on the basis of three component vinylogous Mannich reaction involving a chiral amine[136], which acts as an auxiliary and is removed by hydrogenation.

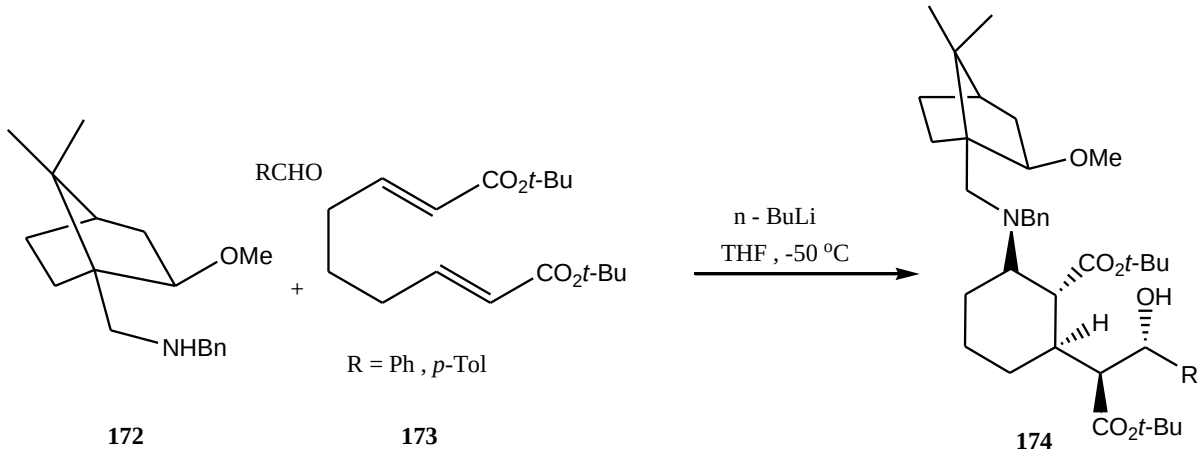



**168** **169** **170** **171**

**Scheme 1.33**

### 1.3.4. Multicomponent reactions intiated by Michael addition

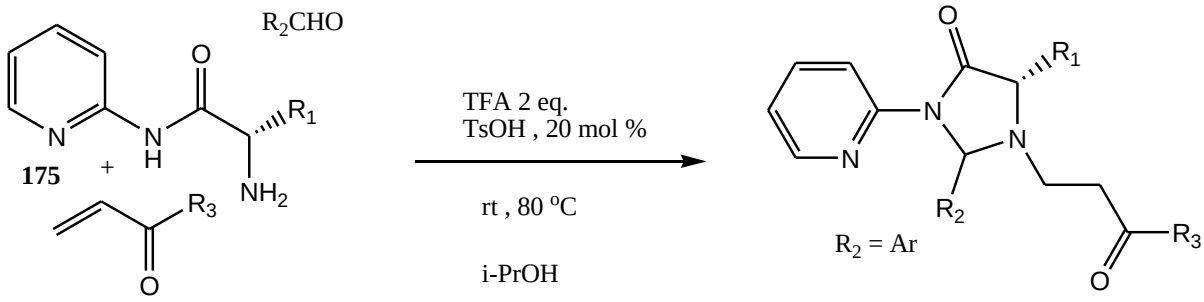
Several multicomponent reactions intiated by Michael addition of carbon nucleophiles have been reported. An asymmetric three component domino reaction intiated by aza-Michael addition has been reported by Node and co-workers[137]. The reaction of N-benzylamine-2(R)-methoxy-(+)-10-bornylamine with benzaldehyde and di-*tert*-butyl 2,6-octadiene-1,8-dioate in the presence of *n*-BuLi afforded a highly functionalized domino product in a good yield. The mechanism involves aza-Michael/Michael/aldol reactions in a domino process.




**172** **173** **174**

**Scheme 1.34**

Wang and co-workers[138] have reported a convenient synthesis of heterocycles **177** through aza-Michael addition reaction. The pyridyl group of a chiral amino amide **175** activated the Michael acceptor **176** under acidic conditions, and acted as a directing group to place the enone and secondary amine in a favourable position for aza-Michael addition.



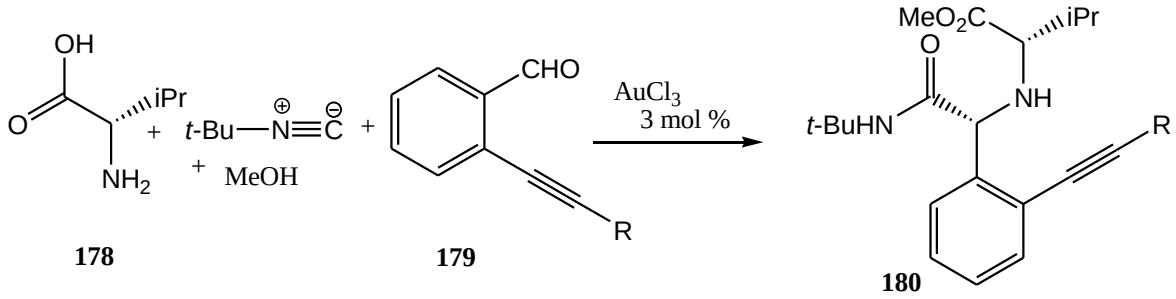

**176** **177**

**Scheme 1.35**

### 1.3.5. Multicomponent Ugi reactions

The Ugi reaction was first described in 1959 and has been more widely studied and used than any other multicomponent reactions[121]. It is a four component reaction of carbonyl compound (usually an aldehyde), amine, an isocyanide and a carboxylic acid (or alcohol) to produce α-amino acid derivatives. The reaction generally proceeds through *in situ* formation of the imine from aldehyde or ketone and primary amine and is followed by the α-addition of isocyanide to this imine and reaction with the carboxylic acid. Subsequent rearrangement affords the α-amino acid derivatives.

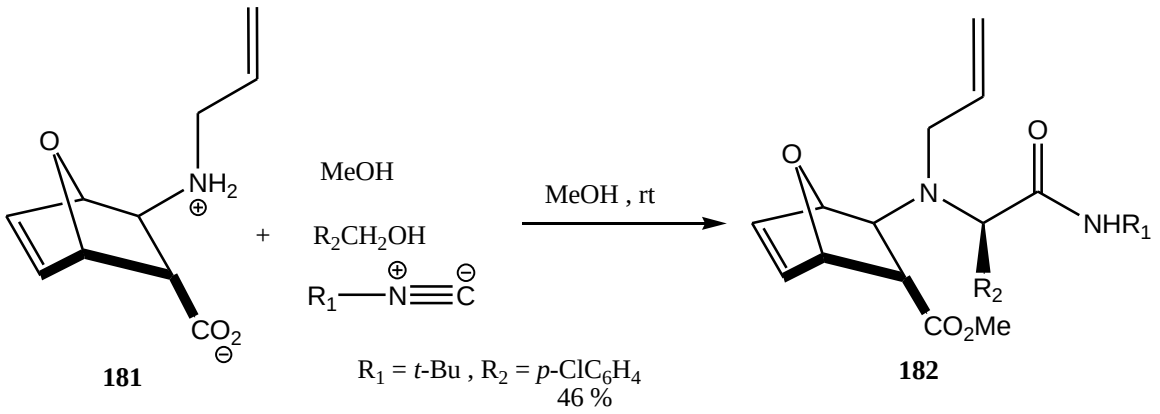
An interesting route to highly fuctionalized chiral dihydroisoquinolines and isoindoles was reported by Dyker *et al*. based on asymmetric four component Ugi reaction involving an amino acid such as L-valine as a chiral auxiliary[139]. The reaction between L-valine, methanol, a benzaldehyde (carrying an alkyne) and *t*-butyl isocyanide gave highly fuctionalised amines. Gold-catalysed intramolecular hydroamination of these products afforded the isoindoles and dihydroisoquinolines.




**178** **179** **180**

**Scheme 1.36**

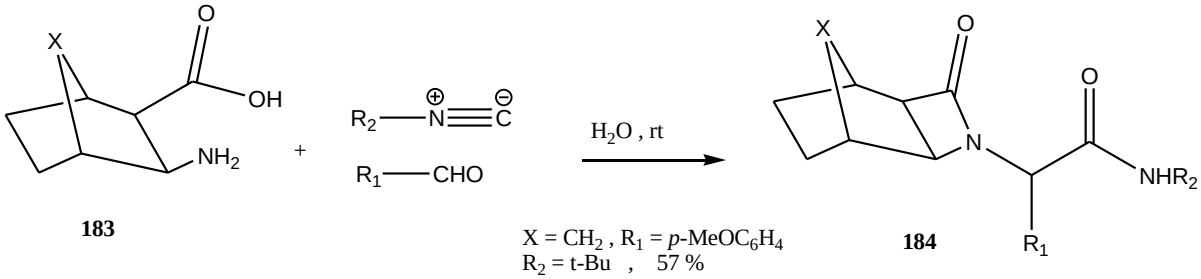
Guanti and co-workers[140] have used optically pure (-)-*N*-allyl-3-amino-7-oxa-[2.2.1]-bicyclohept-5-en-2-carboxylic acid **181** in a four component Ugi reaction. The reaction of acid with aldehydes and isocyanides in methanol at room temperature for 48-72 h resulted in the synthesis of corresponding Ugi products **182**. Subsequent ring opening/ring closing metathesis afforded a series of enantiopure highly functionalised products.




**Scheme 1.37**

The same group has also reported the synthesis of two families of regioisomeric polyfunctionalised cyclohexenols[141] from other oxabicycloheptene based β-amino acids by combining four component Ugi reaction with subsequent Pd-catalyzed ring opening reaction.

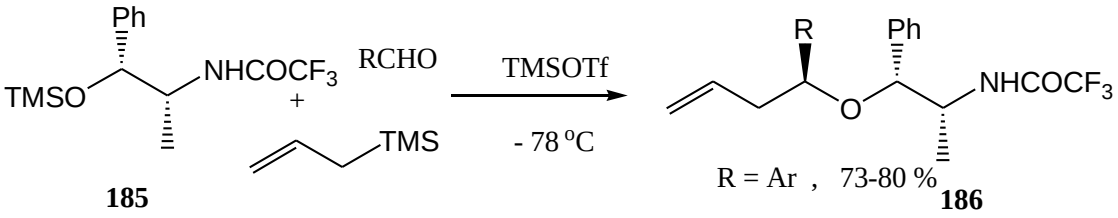
A series of β-amino acids have been used in a three component Ugi reaction with isocyanides and aldehydes to construct β-lactam libraries[142,143]. Water as a solvent has been used in these reactions which showed better reactivity than methanol as a solvent and, with the final products **184** being water insoluble, made the purification easy by simple filtration.




**Scheme 1.38**

### 1.3.6. Multicomponent reactions initiated by allylation reaction

Stereoselective allylation of aldehydes is useful because the resulting chiral homoallylic ethers are important building blocks in the synthesis of a number of biologically active natural products. Tietze *et al.* have developed a stereoselective synthesis of such ethers through a domino three component allylation reaction of aldehydes and allyl trimethyl silane using trimethylsilyl ether **185** as a chiral auxiliary [144-147].

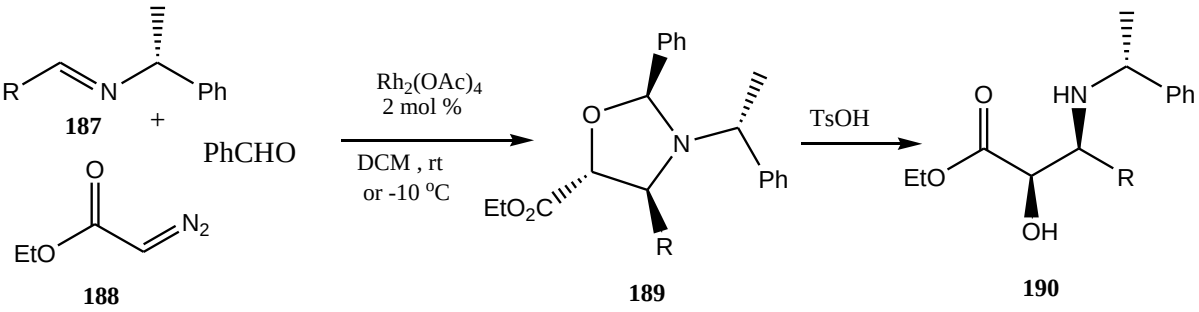



**Scheme 1.39**

### 1.3.7. Miscellaneous multicomponent reactions

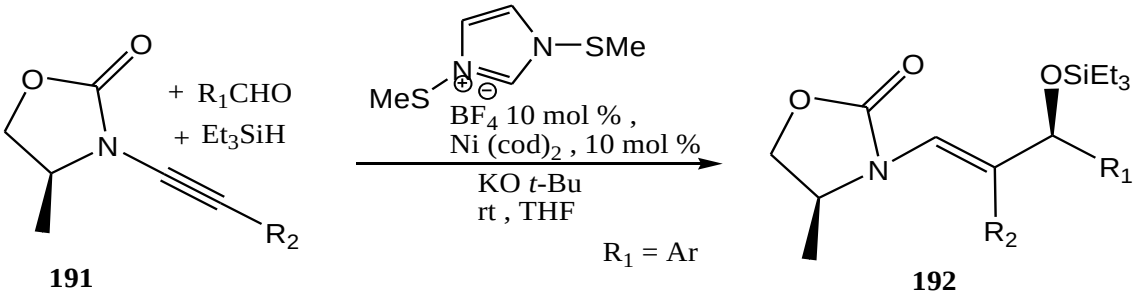
#### 1.3.7.1. Metal catalyzed multicomponent reactions

A Rh(II) catalyzed diastereoselective three component reactions of chiral α-methylbenzylimines, benzaldehyde and ethyl diazoacetate has been used to furnish oxazolines[148]. The oxazolines can be hydrolyzed with TsOH to form *syn*-α-hydroxy-β-amino esters. These compounds can be used in the synthesis of different chiral ligands[149] and also constitute important building blocks in the synthesis of natural products and other biologically active compounds[150,151].



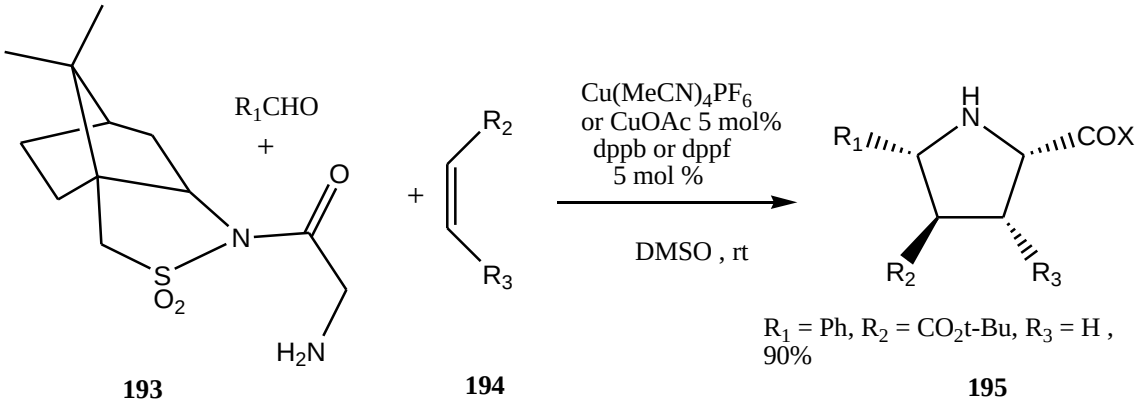

**Scheme 1.40**

Sato and co-workers have reported a nickel catalyzed asymmetric synthesis of γ-siloxyenamides **192**[152]. The reaction involves the diastereoselective coupling of chiral oxazolidinone derived ynamides, aldehydes and triethylsilane.



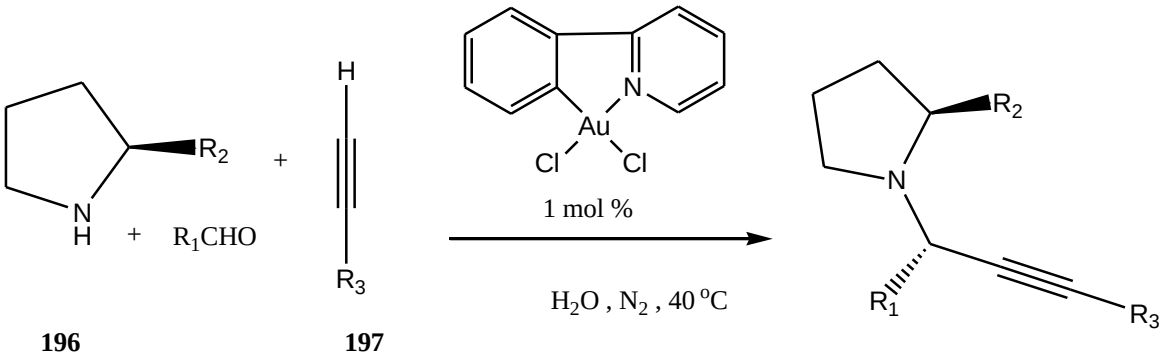

**Scheme 1.41**

Garner *et al.* have reported a copper catalyzed synthesis of highly functionalized pyrrolidines **195** through a three component process[153]. The mechanism involves the reaction between a chiral sultam **193** and aldehyde to form an imine which forms a azomethine ylide which undergoes 1,3-dipolar cycloaddition with activated alkenes to form the products.




**Scheme 1.42**

Che and co-workers have used gold(III) as a catalyst in an asymmetric three component coupling of chiral prolinol derivatives, aldehydes and alkynes to form chiral propargylamines in good yields[154,155].



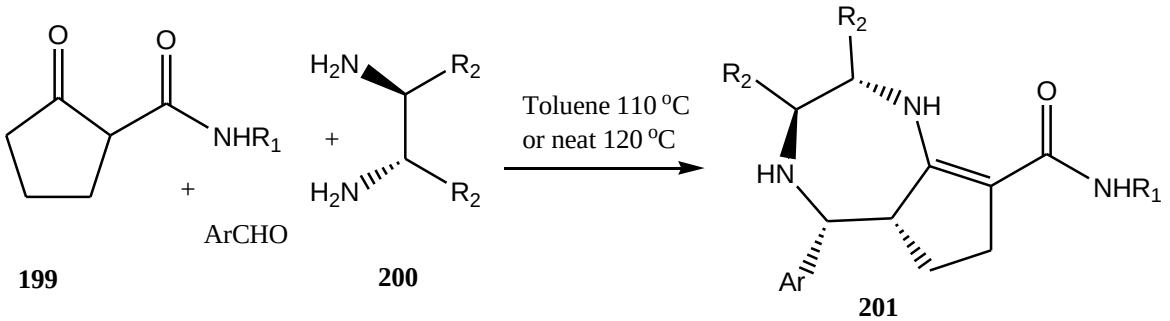

**196** **197** **198**

$R_1$ = Ar, $R_2$ =$CH_2OH$, $CH_2OMe$, $C(Ph)_2OH$
$R_3$ = Ph

**Scheme 1.43**

### 1.3.7.2. Multicomponent reaction of a chiral diamine

Rodriguez and co-workers have reported a multicomponent reaction in which β-ketoamides **199**, aryl aldehydes and cyclic or acyclic 1,2-diamines give 1,4-diazepines in good yields with high diastereoselectivity[156]. In some cases simple heating of the substrate mixture at 120 °C without solvent gave a better result than heating in toluene at reflux. The authors used the same methodology for β-ketoesters in reaction with aryl aldehydes and 1,2-diamines to furnish other 1,4-diazepine derivatives.




**199** **200** **201**

**Scheme 1.44**

As a result of some interesting results with aryl azides (see later), we decided to explore some multicomponent reactions of 2-azidobenzaldehyde, with a particular focus on using the azide to perform further chemistry.

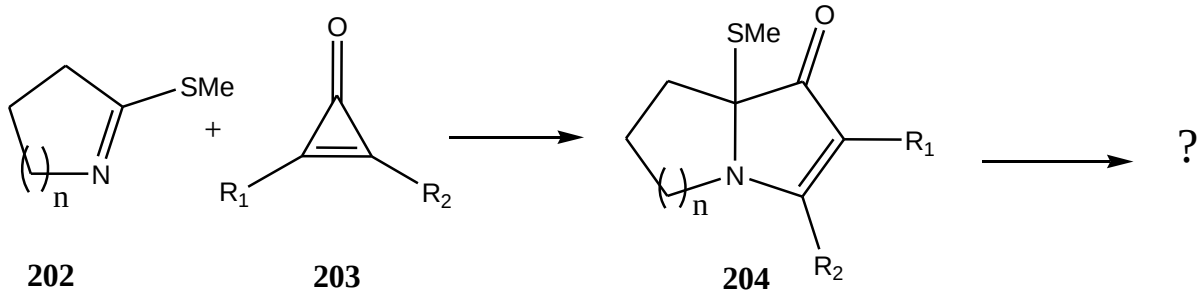
# *Chapter 2;*

# *Results and Discussion*

# 2. Results and Discussion

## 2.1 Aim of the work and outline of discussion

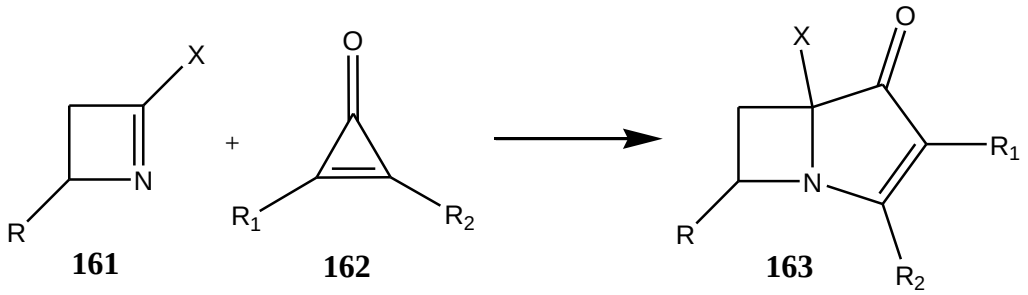
Cyclic imines are known to be reactive towards cyclopropenones[157-160] and 1,3-dipoles[70,161] to form the bicyclic adducts. Some work in the Hemming group has already been done to investigate the reactivity of different cyclic imines towards cyclopropenones and 1,3-dipoles. Based on previous observations in the group the overall aim of this project is to further develop cyclopropenones, which are 1,3-dipole equivalents, and other 1,3-dipoles and to look at their reactions with cyclic imines. For this purpose different cyclic imines will be used and different cyclopropenones and 1,3-dipoles will be tried. The first part of this thesis will describe the synthesis of simple 7-, 6- and 5-membered cyclic imines and the exploration of their reactivity with cyclopropenones, as well as an investigation of the chemistry of their products. The general process is summarised below.




**202** **203** **204**

**Scheme 2.1**

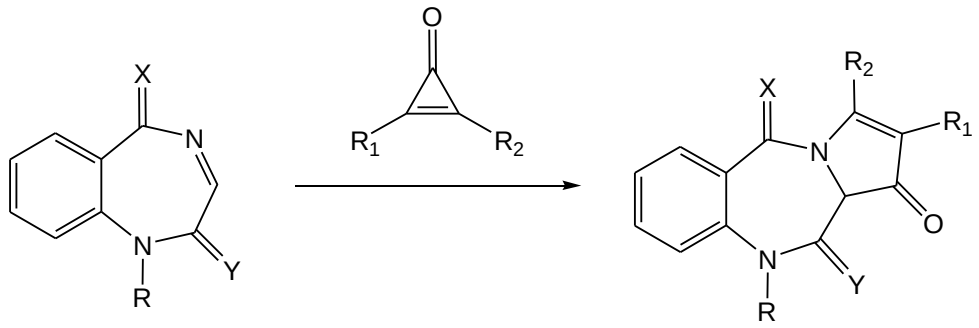
The second part of the discussion will describe the synthesis of four and three membered cyclic imines and their reactivity with cyclopropenones and/or 1,3-dipoles. The reactivity of the bicyclic adducts made from four membered cyclic imines (1-azetines) and cyclopropenones and 1,3-dipoles will also be described.




**161** **162** **163**

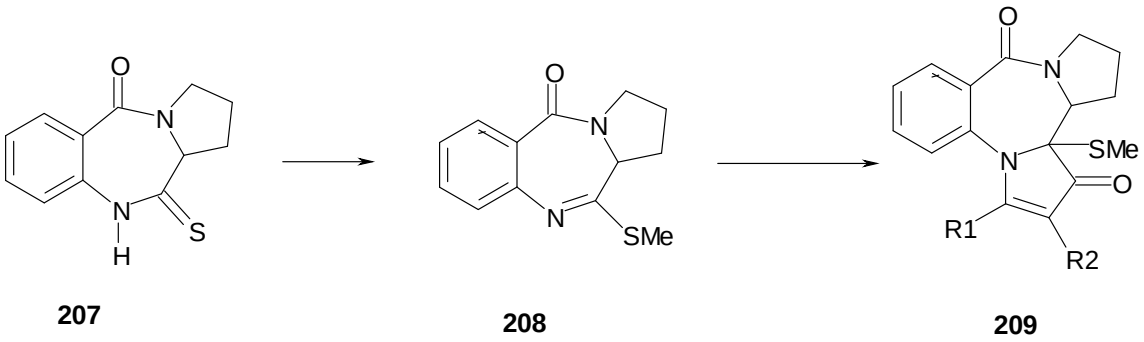
**Scheme 2.2**

The third part of the discussion will deal with a class of cyclic imines made from benzodiazepines and the reactivity of these towards cyclopropenones and 1,3-dipoles with the goal to convert them into pyrrolobenzodiazepines and oxadiazolobenzodiazepines, respectively.




**Scheme 2.3**

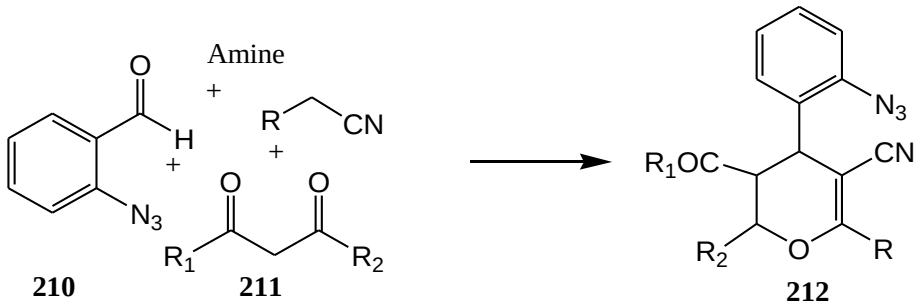
This section of the work will also deal with the use of pyrrolobenzodiazepines themselves as starting materials for the synthesis of tetracyclic benzodiazepines:




**Scheme 2.4**

In all of these reactions, the cyclopropenone, although not a 1,3-dipole, is behaving as if it was an all-carbon 1,3-dipole. Therefore, this thesis will also look at the reactions of several of the above cyclic imines with 1,3-dipoles such as nitrile oxides and nitrile imines. One of the nitrile oxides discussed is 2-azidobenzonitrile oxide, and azide chemistry is a strong theme in the group.

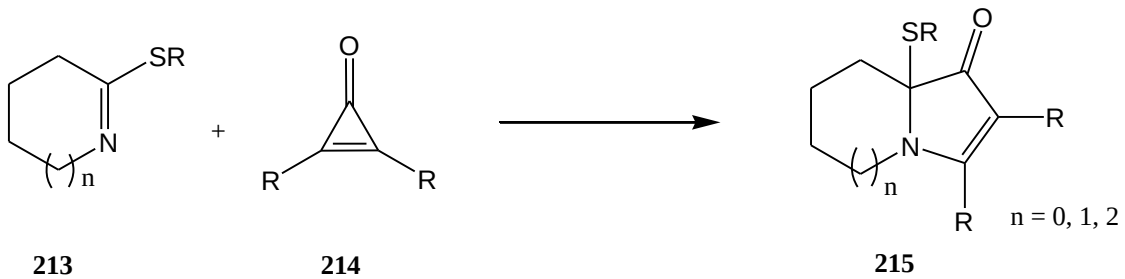
The last part of the discussion will follow this interest and will describe the chemistry of 2-azidobenzaldehyde in multicomponent reactions with cyanides and dicarbonyl compounds, where the presence of azide, carbonyl and nitrile groups in the product can lead to different possibilities such as Staudinger-aza-Wittig sequences to form cyclic imines or azide-nitrile intramolecular cyclization to form a tetrazole ring. An example is shown in scheme 2.5:




**Scheme 2.5**

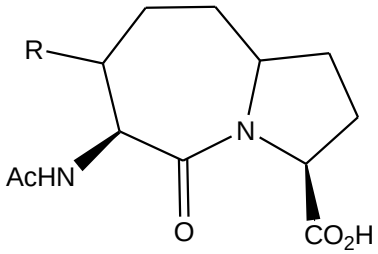
## 2.2 Synthesis and reactivity of 7-, 6- and 5-membered cyclic imines

As the major part of this thesis revolves around the investigation of the reactivity of different cyclic imines with cyclopropenones and 1,3-dipoles, the first task was to synthesize 7-, 6- and 5-membered cyclic imnes and react them with cyclopropenones to give pyrroloazepine, indolizidine and pyrrolizidine respectively as products and to further investigate the reactivity of these products.




**Scheme 2.6**

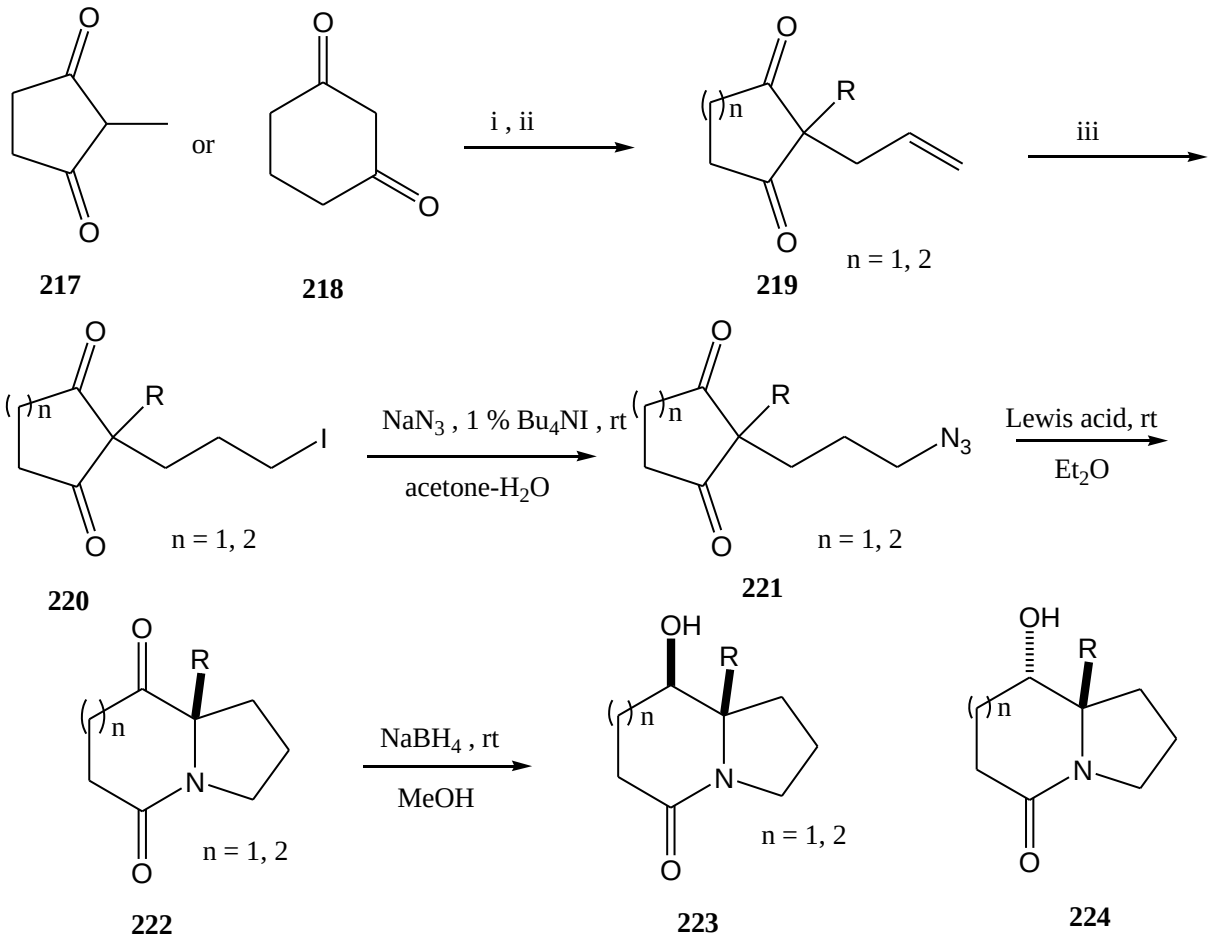
The reason for selecting these systems was that pyrroloazepines, indolizidines and pyrrolizidines are naturally occurring alkaloids which exhibit pharmacological properties and have attracted attention of synthetic chemists [162-164]. Pyrroloazepines such as bicyclic lactams **216** are believed to have potential to be used as protease inhibitors which are implicated in a range of diseases such as rheumatoid arthritis and cystic fibrosis[165,166]. Indolizidines and pyrrolizidines are potentially important in the treatment of viral infections (such as HIV), diabetes (type II), cancer lines and of several neurological disorders.




**216**

**Fig. 2.1**

Syntheses of pyrroloazepines, indolizidines and pyrrolizidines have been reported frequently in the literature. For example, Marsden and co-workers[167] have reported the synthesis of indolizidines and pyrroloazepines via an intramolecular Schmidt reaction of azido 1,3-diketones which were prepared from 2-methylcyclopentane 1,3-dione or cyclohexane 1,3-dione, as shown below.



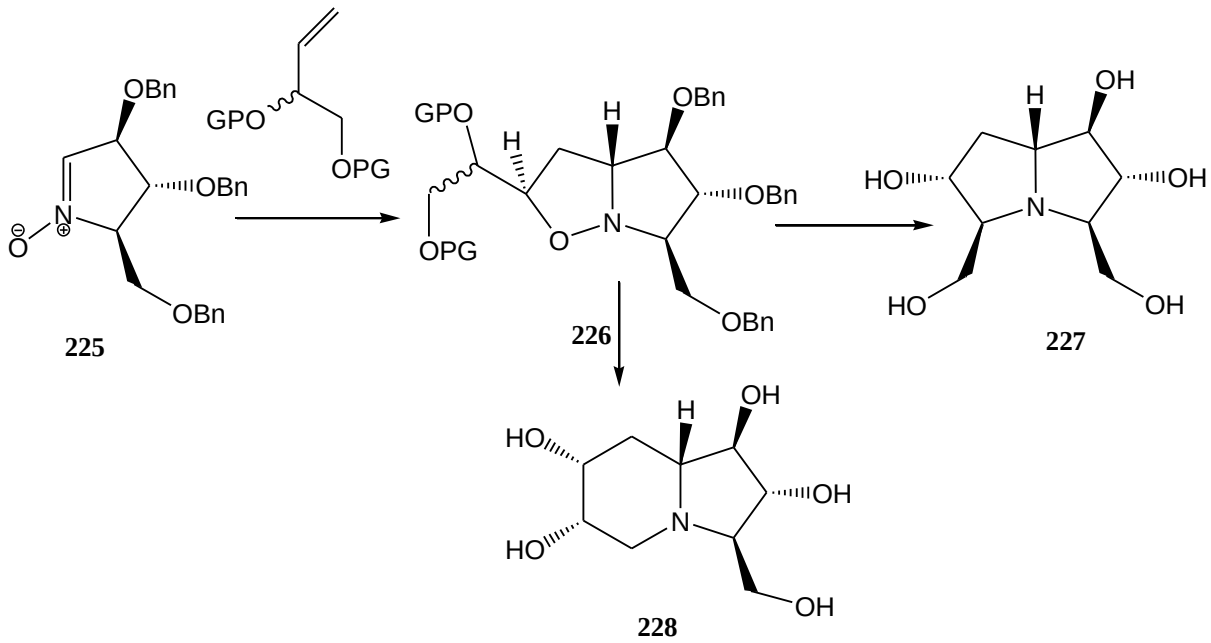

i = 5M NaOH, MeI, or BnBr, 65 or 100 $^{o}$C respectively. ii = 1N NaOH, 1% $Bu_4NI$, allyl bromide, rt.

iii = 1.2 eq. $BH_3.Me_2S$, 2.5 eq. cyclohexene, THF 0 $^{o}$C, then to rt then NaOAc-MeOH, $I_2$ ,rt.

**Scheme 2.7**

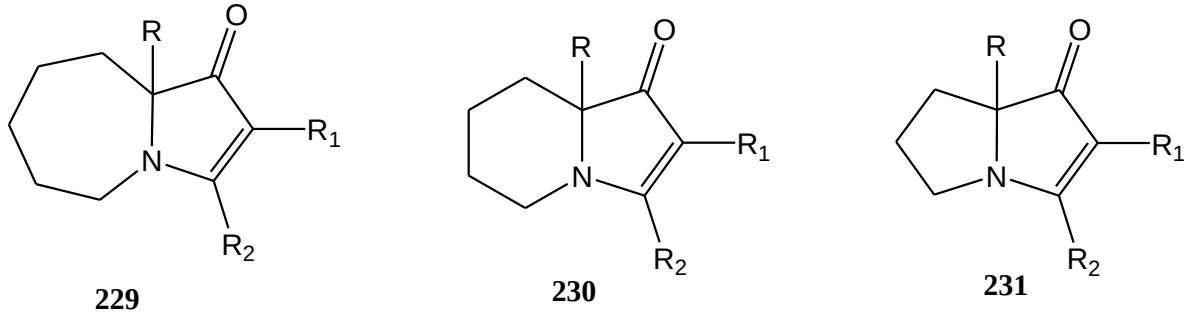
Tamayo and co-workers have reported the synthesis of pyrrolizidines **227** and polyhydroxylated indolizidines **228** via pyrroloisoxazolidines **226** produced as a result of 1, 3-dipolar cycloaddition of nitrones with 3-buten-1,2-diol derivatives which were prepared chemoenzymatically. N-O cleavage by using Zn/AcOH and deprotection of protecting groups gave the target molecules[168].

Li *et al.* have also used aza-sugar nitrones to produce indolizidines containing an amino group, using an intramolecular cycloamidation[169].




**Scheme 2.8**

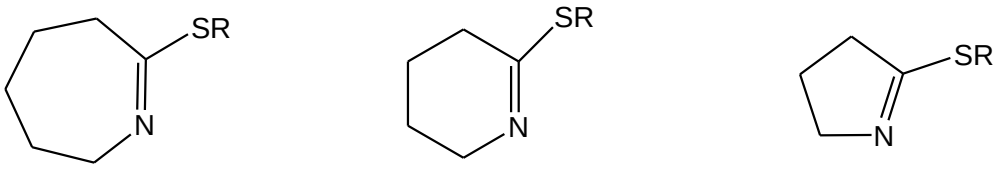
In our approach, based on the previous work done in the group, pyrroloazepines, indolizidines and pyrrolizidines were accessed via reaction of cyclic imines and cyclopropenones. This approach would produce the compounds of general structure **229-231**, which have been made once before in the group, but whose chemistry had not been explored. The first task of this PhD project was to resynthesize these compounds, optimize the reactions and explore the chemistry of the adducts **229-231**.




**229** **230** **231**

**Fig. 2.2**

This necessitated the synthesis of the cyclic imines **232-234** shown in figure **2.3** below, which are accessible from the readily available corresponding lactams.




**232** **233** **234**

**Fig. 2.3**

## 2.2.1. Synthesis of 7-, 6- and 5-membered cyclic imines

Synthesis of these imines started with the thionation of corresponding lactams i.e. ε-caprolactam, valerolactam and 2-pyrrolidone respectively.

### 2.2.1.1. Thionation of lactams

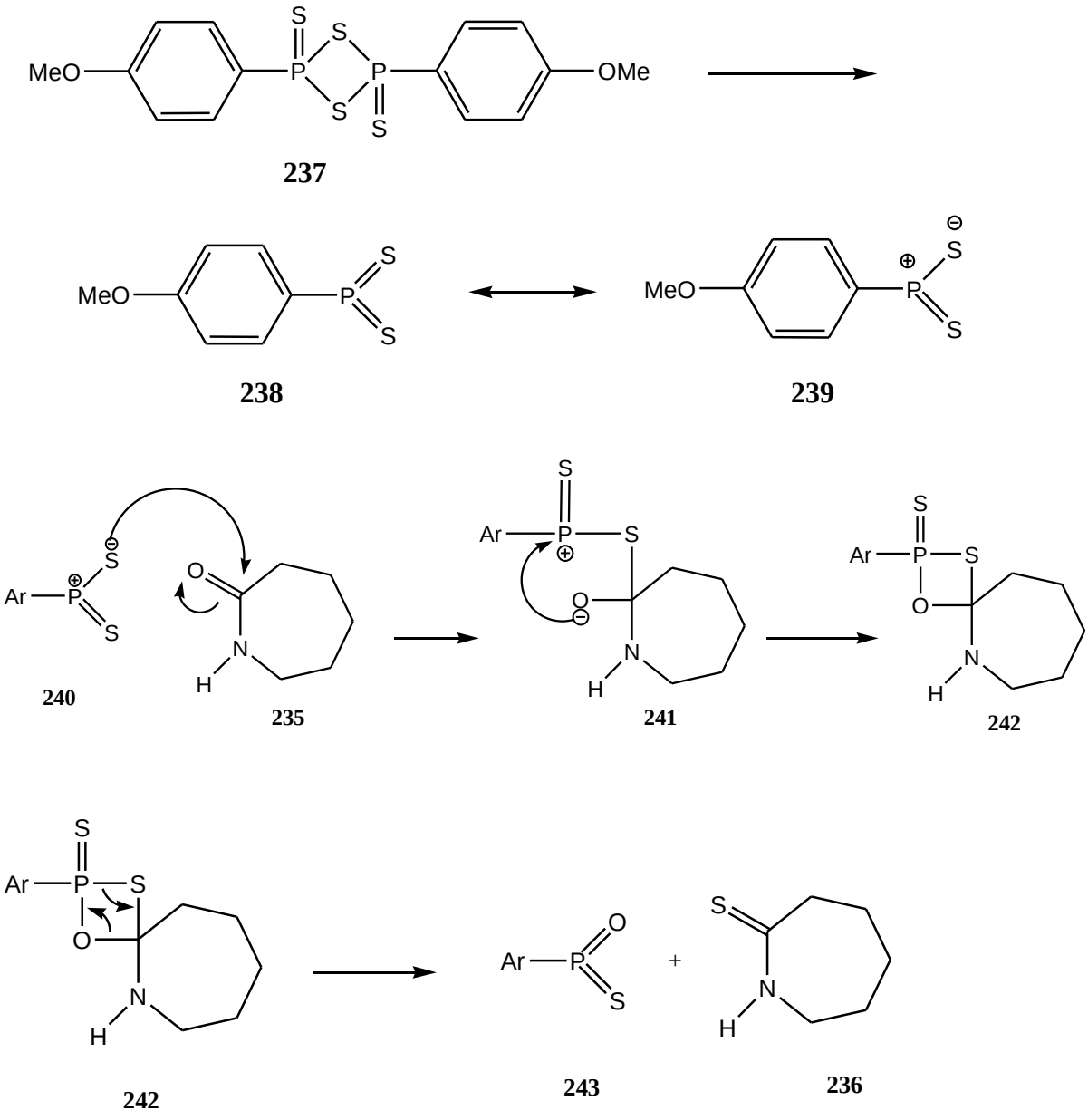
Thionation of the lactams was achieved using Lawesson's reagent, which has been widely used since 1978[170-172] as a thionating reagent. It requires only mild conditions, gives high yields and is commercially available. There is another reagent, phosphorus pentasulfide[170], which has been used for thionation but recently Bergman[173] *et al.* reported a $P_4S_{10}$.pyridine complex as a thionating reagent which can be used in more polar solvents like DMSO, DMF and at higher temperatures, with an easy non-chromatographic work-up. This complex will be discussed in detail in a later part of this discussion.

ε-Caprolactam was thiated with Lawesson's reagent, the reaction yielded the corresponding thiolactam in 95 % yield.


**235** **236**

**Scheme 2.9**

Lawesson's reagent produces a ylidic intermediate as a result of breaking the sulfur-phosphorus bond at higher temperature. This specie, acting as a nucleophile, attacks the carbonyl of the lactam and after rearrangement via a four membered complex yields the thiolactam.

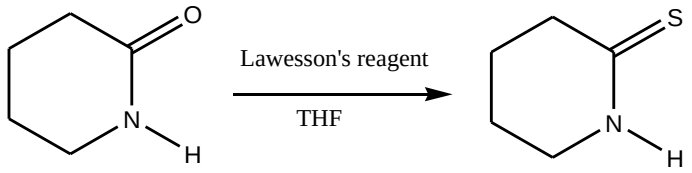



**Scheme 2.10**

The structure of ε-caprothiolactam was confirmed by IR and NMR. $^{1}H$ NMR showed signals in ratio of 2:2:2:2:2:1 for five sets of $CH_2$ and one NH which appeared at 9.19 ppm. $^{13}C$ NMR

showed the distinctive peak of C=S at 210.31 while IR showed the thiocarbonyl signal at 1552 $cm^{-1}$ confirming the product as thiolactam.

Valerolactam was thionated by using the same method as for ε-caprolactam to get the valerothiolactam as white crystals in 84 % yield.

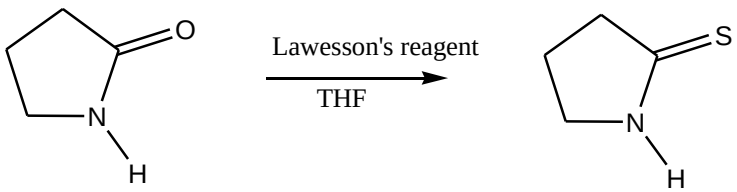



**244** **245**

**Scheme 2.11**

Spectroscopic analysis showed the secondary thioamide peak at 9.53 ppm and the $CH_2$ neighbouring C=S at 2.82 ppm as a triplet, with the rest of the protons for the other $CH_2$ groups appearing as multiplets. $^{13}C$ NMR peaks for the four $CH_2$s appeared in the region between 20-45 ppm while the C=S peak appeared at 202.11 ppm to confirm the thionation of the valerolactam.

Pyrrolidine-2-one was thionated with Lawesson's reagent in THF to get the product in 90 % yield as white crystals.




**246** **247**

**Scheme 2.12**

The product showed the expected spectroscopic characteristics, for example, the presence of a broad signal at 3139 $cm^{-1}$ in the IR spectrum with a broad peak at 8.74 ppm in the $^1H$ NMR spectrum to confirm the presence of the thioamide group. A triplet at 3.63 ppm in the $^1H$ NMR spectrum confirms the $CH_2$ neighbouring the thioamide and a triplet at 2.92 ppm

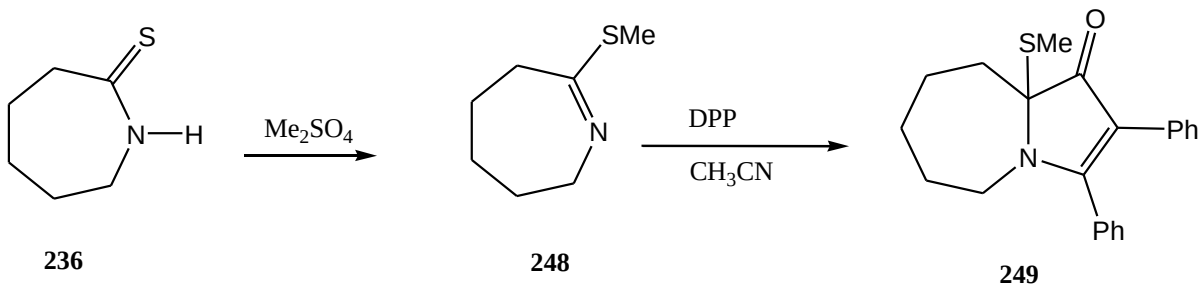
confirmed the $CH_2$ next to C=S. $^{13}C$ NMR showed a peak at 206.07 ppm to confirm the presence of the thiocarbonyl.

## 2.2.2. Reactivity of 7-, 6- and 5-membered cyclic imines with cyclopropenones.

Thiolactams were alkylated with dimethyl sulfate to give the crude cyclic imines which were used directly in reaction with cyclopropenones. These cyclic imines were found to be volatile and unstable so, it was decided to not purify them and use them directly for reaction with cyclopropenones. It is worth noting at this point that the alkoxy compounds, whilst stable, were unreactive. This thesis focuses entirely on alkylthio compounds.

### 2.2.2.1 Synthesis of 2-methylthio-1-azepan and its reactivity with diphenylcyclopropenone.

Alkylation of azepan-2-thione with dimethyl sulfate resulted in the synthesis of the desired cyclic imine. Work up was done with potassium carbonate, and diphenylcyclopropenone was added to a solution of the imine in acetonitrile. Compound **249**, the desired bicyclic adduct was isolated in 59 % yield, a significant improvement on the previous results in the group which had used Meerwein's reagent to alkylate with attempted isolation of the imine.




**236** **248** **249**

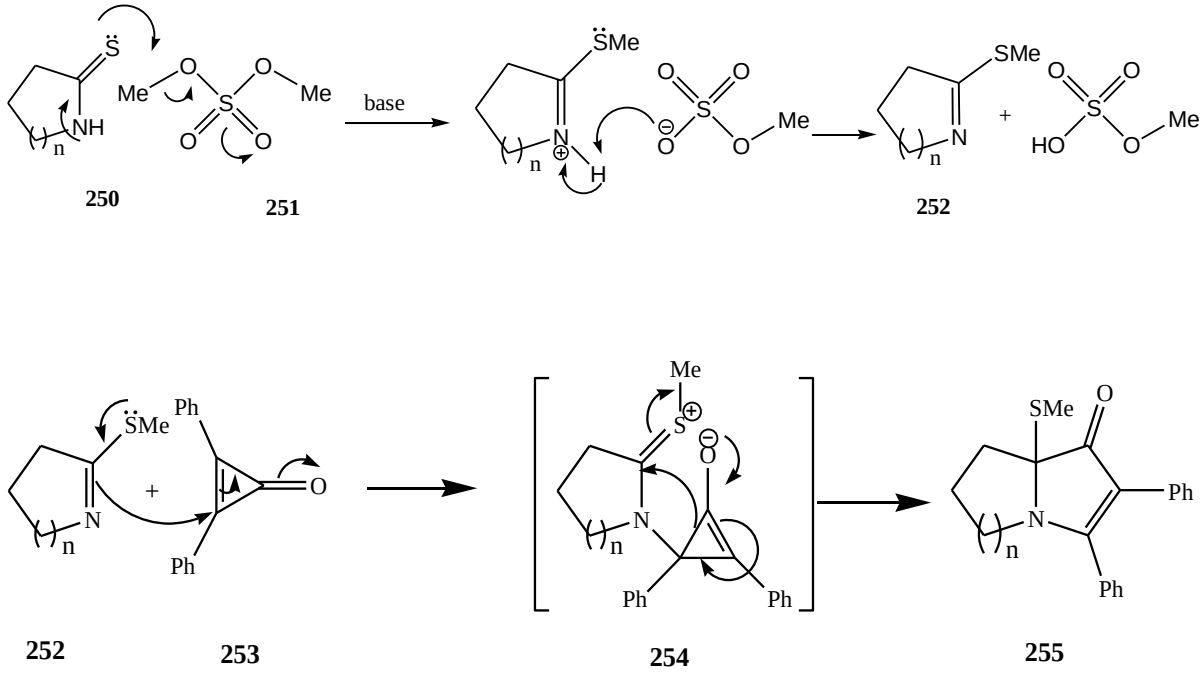
**Scheme 2.13**

Spectroscopic analysis confirmed the synthesis of compound **249**. The $^1H$ NMR spectrum showed ten aromatic protons in the region between 7.53-6.98 as four sets of multiplets confirming the presence of two phenyl groups. The ten protons of the five aliphatic ring $CH_2$s appeared between 3.82-1.01 while disappearance of the thioamide proton and appearance of a

singlet at 1.97 integrating for three hydrogens confirmed the presence of thiomethyl moiety in the molecule.

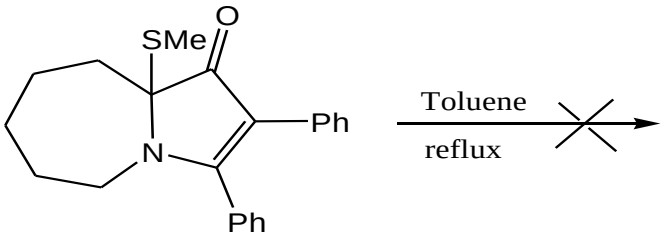
The $^{13}C$ NMR spectrum showed six CH carbons and four quaternary carbons between 113.21-174.29, and a peak at 197.63 ppm for the presence of carbonyl group. Five peaks for $CH_2$s appeared between 43.32 to 23.95 ppm while a peak at 11.56 confirmed the presence of methyl group. A consistent HRMS measurement confirmed the assignment.

Alkylation of thiolactam involves an attack from the thiolactam sulfur to dimethyl sulfate to form the imine. The presence of the electron donating thiomethyl group increases the nucleophilicity of the nitrogen; as a result nucleophilic attack from nitrogen to cyclopropenone, which is behaving as a Michael acceptor, allows an intermediate **254** to be proposed. The enolate of intermediate **254** undergoes an intramolecular attack on the electrophilic carbon followed by ring expansion of the cyclopropenone to form the product **255**.




**Scheme 2.14**

After confirming the product as 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one, the next step was to investigate its reactivity.



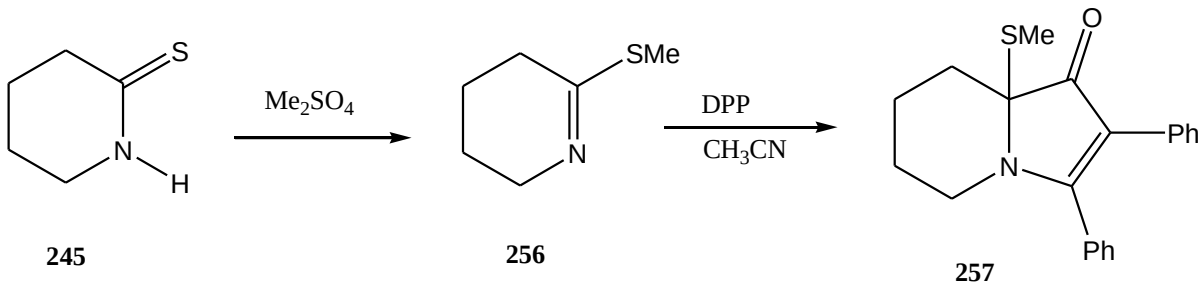

**249**

**Scheme 2.15**

On the basis of a previous observation in the group, it was envisaged that this compound might undergo a heat promoted reaction, but when it was subjected to boiling toluene or xylene it was found to be very stable and no product could be found even after 72 hours of heating. Heating in other solvents such as dichlorobenzene similarly showed no reaction.

### 2.2.2.2 Synthesis of 2-methylthio-1-piperidine and its reactivity with diphenylcyclopropenone.

Valerothiolactam was alkylated with dimethyl sulfate using the same method as for the synthesis of 7-membered cyclic imines described in section 2.2.2.1 and diphenylcyclopropenone was added to the mixture of imine to form the product, 6-methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one, in 55 % yield.



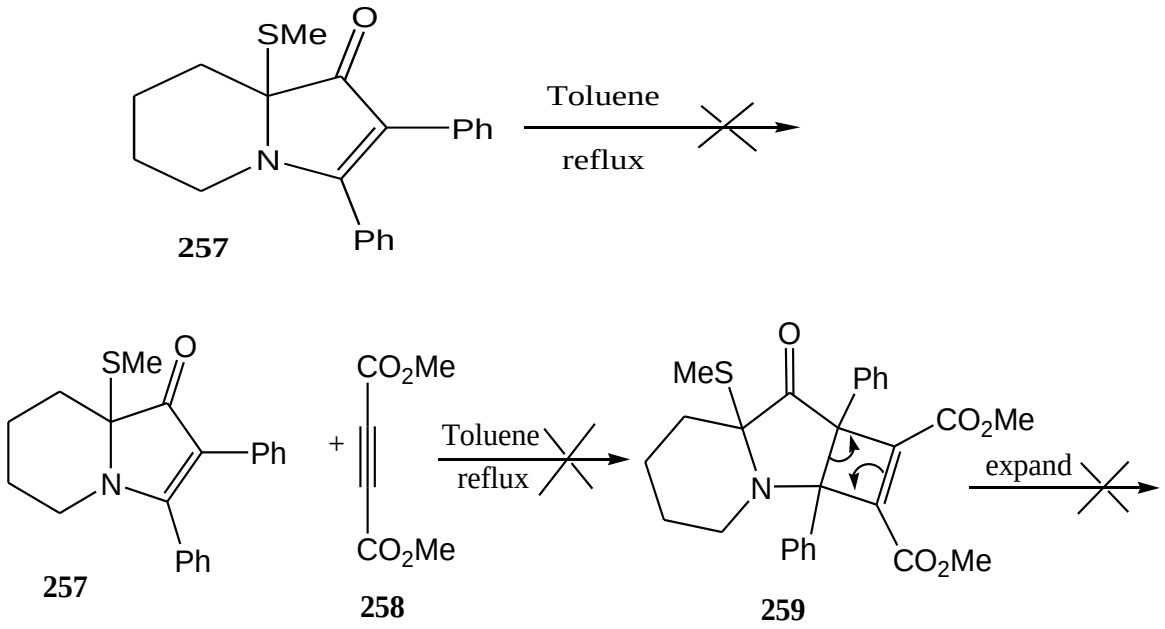

**245** **256** **257**

**Scheme 2.16**

The product showed the expected spectroscopic characteristics; for example the presence of ten aromatic protons between 7.00-7.52 ppm and eight protons of four $CH_2$s between 3.65-1.29 ppm in the $^1H$ NMR spectrum. A singlet at 1.98 showed the three protons of $SCH_3$, whereas the thioamide NH group had disappeared. $^{13}C$ NMR spectroscopy confirmed the

eight aromatic signals between 125.23 to 131.65 and the quaternary carbon of the bridgehead was seen at 72.19 ppm. A peak at 198.75 ppm confirmed the presence of the carbonyl which was also confirmed by the IR spectrum with a peak at 1655 $cm^{-1}$. Mass spectrometry confirmed the exact mass of the compound.

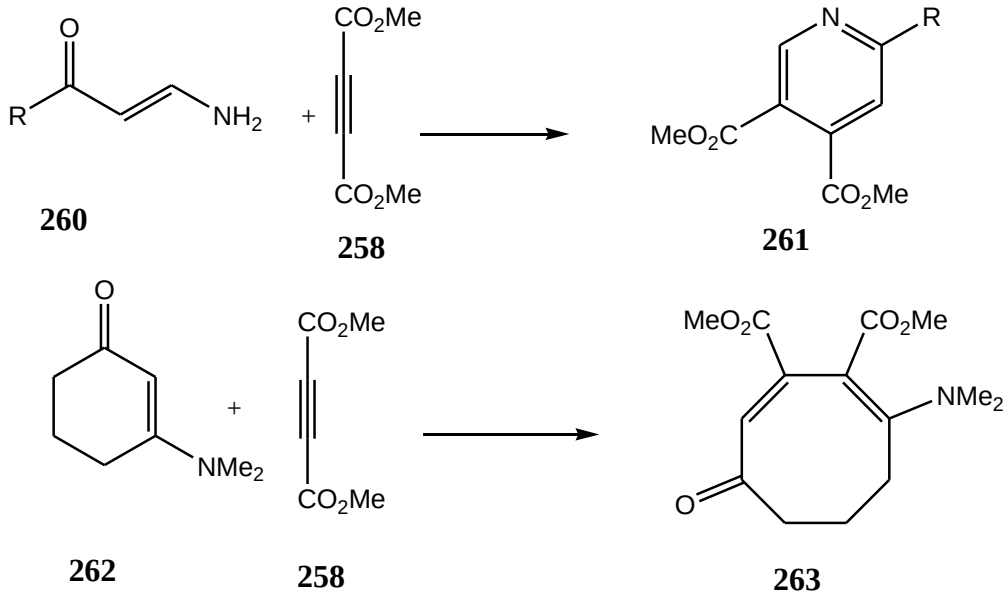
Next, the reactivity of the adduct **257** was explored by heating it in boiling toluene as other workers in the group had observed a one-spot to one-spot transformation under such conditions. However, on this occasion, the compound **257** was found to be very stable and the starting material was fully recovered after purification with column chromatography. Heating in the higher boiling xylene gave similar results, whilst even higher boiling solvents e.g. dichlorobenzene resulted in degradation of compound **257**.




**Scheme 2.17**

In another attempt, also showed in scheme **2.17**, above, adduct **257** was mixed with DMAD and heated in toluene in order to investigate its potential [2+2] cycloaddition reactivity with DMAD. However, no product was observed and the starting material was recovered after the purification. This concept builds on the work of Stanovnik[174] who has shown that acyclic

enaminones **260** and cyclic enaminones **262** react with DMAD to form ring expanded products **261** and **263** in 70 and 73 % after [2+2] cycloaddition, as shown in scheme **2.18**.



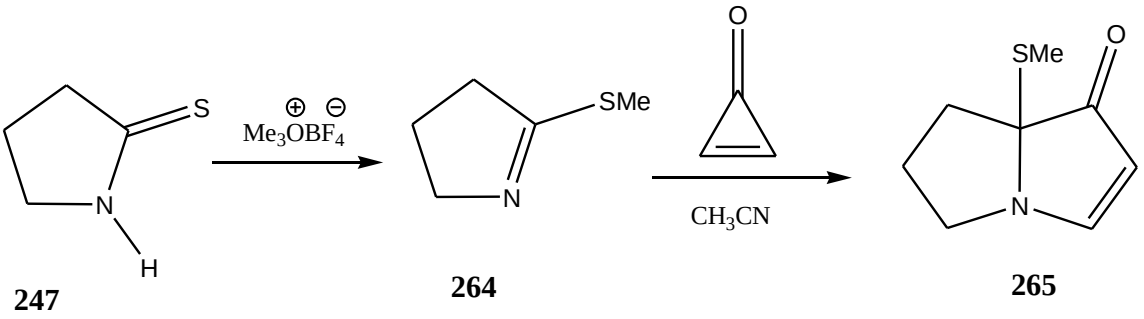

**Scheme 2.18**

It was assumed that alkene of compound **257** is unreactive because of it being in a more conjugated and stable system. For this reason, a non-phenyl substituted system was synthesized using the parent cyclopropenone rather that DPP, as described below.

### 2.2.2.3 Synthesis of 5-(methylthio)-3,4-dihydro-2*H*-pyrrole and its reactivity with cyclopropenone.

The alkylation of pyrrolidine-2-thione was performed with Meerwein's reagent in DCM and work up was done with aqueous potassium carbonate to release the imine from its $HBF_4$ salt. This imine was also found volatile and was used as crude for cycloaddition with cyclopropenone. Crude cyclopropenone acetal (available from another worker in the group) was treated with Amberlyst 15 in acetone to perform a deprotection and generate cyclopropenone. After 30 min. of stirring, deprotection was completed, as monitored by TLC, and confirmed by IR spectroscopy. The resulting mixture was added to the mixture of 2-methylthio-1-pyrroline in dry acetonitrile to give the product 7a-(methylthio)-5,6,7,7a-

tetrahydro-pyrrolizin-1-one **265** in 18 % yield as a yellow oil. Some attempts were made to get a better yield but due to the unstability of both the cyclopropenone and the imine, it was impossible to improve the yield.



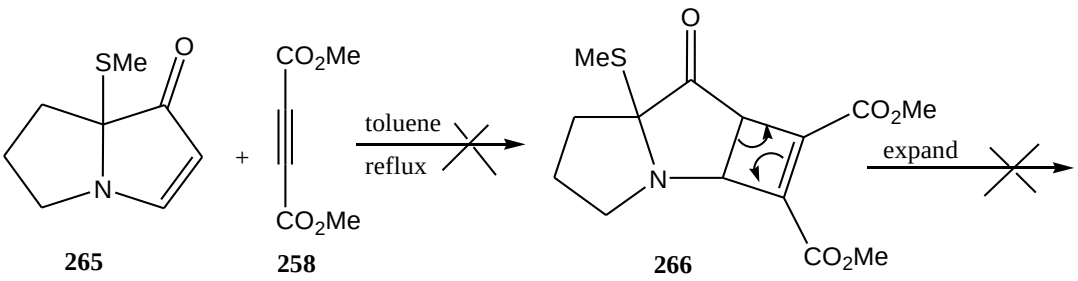

**247** **264** **265**

**Scheme 2.19**

The structure of the product **265** was confirmed by spectroscopic analysis. The $^{1}H$ NMR spectrum shows signals for the protons at β and α positions of the unsaturated carbonyl at 7.77 and 5.35 ppm respectively, both as doublets with a coupling constant 3.5 Hz. The signals for six aliphatic protons appeared between 1.85 to 3.56 ppm whilst one singlet at 1.96 ppm integrated as three protons confirming the presence of the thiomethyl moiety.

The $^{13}C$ NMR spectrum showed the carbonyl signal at 203.54 ppm and signals for β and α carbon of the unsaturated carbonyl at 169.00 and 105.24 ppm, respectively. Three peaks for the $CH_2$s appear between 48.46 to 27.07 ppm and a peak at 11.84 confirmed the thiomethyl moiety. The IR spectrum confirmed the presence of carbonyl with a peak at 1681 $cm^{-1}$.

It was anticipated that our system, now lacking phenyl groups, might react with DMAD to do the cycloaddition shown below, as precedented by the work shown in scheme **2.18**, above, developed by Stanovnik.




**265** **258** **266**

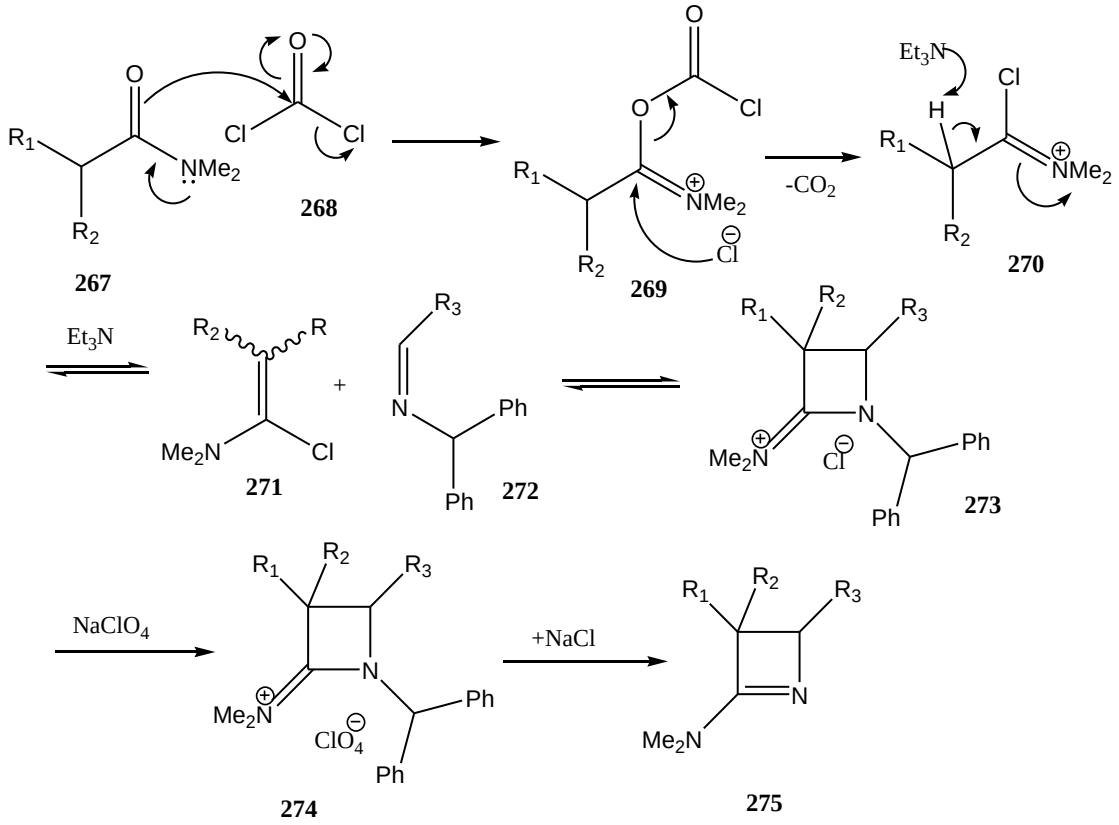
**Scheme 2.20**

So, compound **265** was mixed with DMAD in acetonitrile and heated at reflux for 12 hours; however, no product was formed although starting material could not be recovered because of its decomposition. The failure of 5-, 6- and 7-membered cyclic imine cyclopropenone adducts to react meant that a change of direction was taken. Next, we turned our focus towards smaller ring systems like 1-azetines and 1-azirines, 4-membered and 3-membered cyclic imines respectively. Explored was their reactivity against cyclopropenones and 1,3-dipoles and the chemistry of the products (bicyclic systems) that were expected to be formed once the 1-azetines and 1-azirines had reacted was also investigated.

## 2.3 Synthesis and reactivity of 4- and 3-membered cyclic imines.

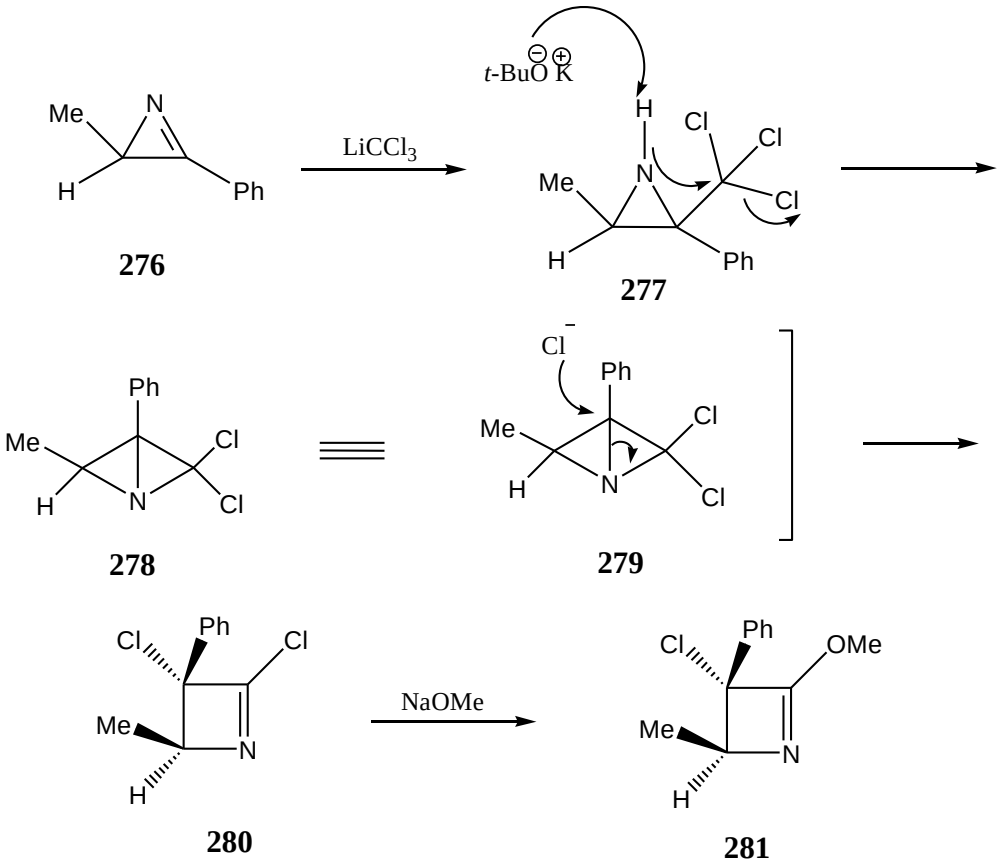
### 2.3.1 Synthesis of 1-azetines

Several synthetic routes to 1-azetines have been described in the literature. Treatment of phosgene **268** with dimethylamides **267** in the presence of triethylamine gives α-chloroenamines **271** which upon forming benzhydryl imines produce 2-dimethylamino-1-azetines **275** after ion exchange, hydrogenation and basification[175].




**Scheme 2.21**

Some photochemical syntheses[176,177] of 1-azetines have been reported via photocyclization of substituted alpha-dehydrophenylalanines but this has got some limitations. Nucleophilic addition of trichloromethyllithium to 1-azirine **276** has resulted in the synthesis of 2,3-dichloro-1-azetine **280** after the basification with potassium *tert*-butoxide whereas treatment with sodium methoxide resulted in the synthesis of 2-methoxy-1-azetines **281**[178,179].




**Scheme 2.22**

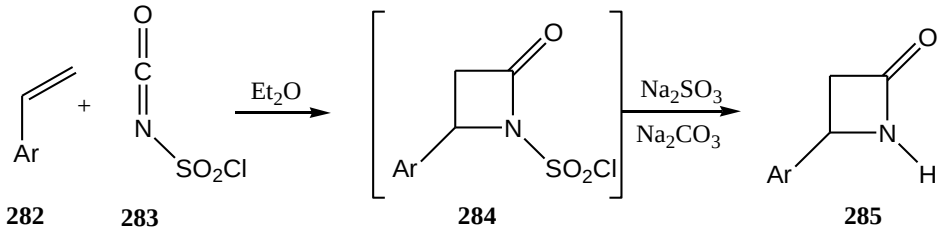
Thermal rearrangement of 1-(alkylthio)-cyclopropyl azides leads to 2-alkylthio-1-azetines[180] whereas thermal ring expansion of cyclopropyl azides led to simple alkyl and aryl-1-azetines[181,182]. 1-Azetines are formed as a result of O-alkylation and S-alkylation of azetidine-2-one and azetidine-2-thione (formed after thionation of azetidine-2-one) with trialkylfluoro tetraborates followed by basification [183-186], a route used successfully by other workers in the group.

Keeping in view the previous studies, it was decided to adopt the latter route for the synthesis of 1-azetines.

## 2.3.1.1 Synthesis of 4-aryl-1-azetines

### 2.3.1.1.1 Synthesis of 4-aryl-azetidinones

As a first step towards the synthesis of 4-aryl-1-azetines, it was necessary to first synthesize 4-aryl-1-azetidine-2-ones which were easily accessed using a literature method [187-190]. A [2+2] cycloaddition between a styrene and chlorosulfonyl isocyanate resulted in the synthesis of a chlorosulfonyl β-lactam which was reduced by sodium sulfite and sodium carbonate to the 4-aryl-1-azetidine-2-one.




**282** **283** **284** **285**

Ar = a = phenyl, b = tolyl, c = naphthyl

**Scheme 2.23**

Spectroscopic characteristics of the compounds **285a-c** evidenced the structures of the azetidinones. 4-Phenyl-1-azetidine-2-one was obtained in 79 % yield as a white solid.

The $^{1}H$ NMR spectrum of **285a** showed five aromatic protons at 7.34 ppm as a multiplet and a broad peak at 6.97 ppm confirming the amide group in the compound, other peaks confirmed the ring formation showing the benzylic proton as a doublet of doublets at 4.67 ppm with $J$ = 5.2 and 2.3 Hz confirming the coupling with both hydrogens of $CH_2$ in the ring. Two signals at 3.38 and 2.80 ppm respectively confirmed two protons of $CH_2$ of the ring with a geminal coupling constant $J$ = 14.8 Hz. The $^{13}C$ NMR spectrum showed a peak at 168.48 ppm for the carbonyl group, four aromatic signals, a peak at 50.15 for CH and a peak at 47.60 for $CH_2$. The IR spectrum showed a peak at 1705 $cm^{-1}$ to confirm the carbonyl group and mass spectrometry further confirmed the structure of the compound.

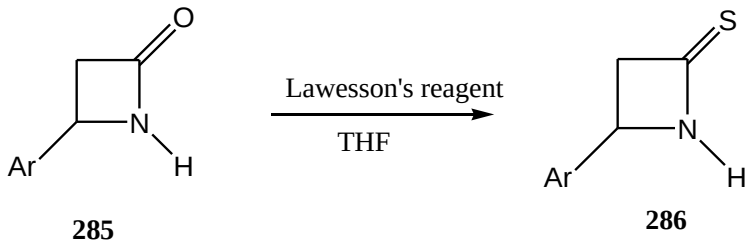
Compound **285b** was produced in 83 % yield as a white solid showed the expected spectroscopic characteristics. The $^{1}H$ NMR spectrum showed four aromatic protons as two doublets between 7.20-7.27 ppm. A broad peak at 6.74 confirmed the NH and a doublet of

doublets at 4.69 ppm confirmed the benzylic proton of the ring. Two signals at 3.42 and 2.84 ppm respectively confirmed two protons of $CH_2$ of the ring and a singlet at 2.37 ppm integrating to three protons confirmed the methyl of tolyl moiety. The $^{13}C$ NMR spectrum evidenced the presence of a carbonyl group with a peak at 168.63 ppm and tolyl group with four aromatic peaks and a peak at 21.19 ppm for methyl group. Ring formation was evidenced by the presence of a signal at 50.37 for CH and another at 47.93 for $CH_2$. The IR and MS data further confirmed the structure of 4-tolyl-azetidinone.

Spectroscopic analysis of 4-naphthyl-1-azetidine-2-one **285c** (obtained in 64 % yield as a white solid), confirmed the structure of the compound. The $^{1}H$ NMR spectrum showed signals for seven aromatic protons and a broad signal at 6.69 ppm for the amide moiety. A doublet of doublets at 4.85 ppm confirmed the presence of the benzylic proton, whereas the two protons of $CH_2$ were evidenced by two different signals at 3.52 and 2.84 ppm respectively. In the $^{13}C$ NMR spectrum the carbonyl group was evidenced by a peak at 168.4 ppm and ten signals in aromatic region confirmed the naphthyl moiety. Peaks at 50.58 ppm and 47.90 ppm respectively confirmed the CH and $CH_2$ of the ring. The IR spectrum showed a peak at 1709 $cm^{-1}$ to further confirm the presence of a carbonyl group.

### 2.3.1.1.2 Synthesis of 4-aryl-1-azetidine-2-thiones

To convert azetidines to 1-azetines it was necessary to do the thionation of azetidines first and then do thioalkylation to produce 1-azetines. Alkoxy azetines are known to be less stable than thioalkyl azetines[157] and hence it was decided to thionate the azetidines. Lawesson's reagent was selected to use for thionation. Although there are some other thionating reagents in use which will be discussed later in this thesis, Lawesson's reagent was selected because of its commercial availability and high yields.




**285** **286**

Ar = phenyl , tolyl , naphthyl

**Scheme 2.24**

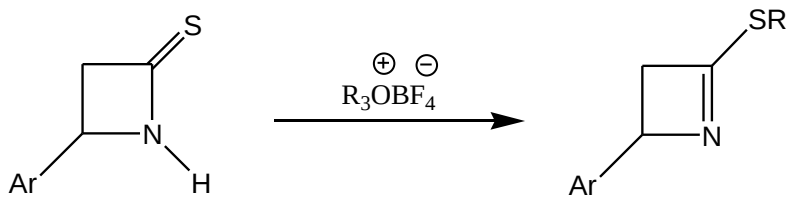
Thionation was conducted in dry THF and thionation of 4-phenyl-1-azetidine-2-one gave 48 % yield of thiolactam as a white solid. The structure of 4-phenyl-1-azetidine-2-thione was confirmed by IR and NMR spectroscopic analysis. The $^{1}H$ NMR spectrum showed a shift in the amide peak from 6.97 ppm to 8.28 ppm while the presence of the four-membered ring was confirmed by the doublet of doublets at 5.18 ppm indicating the benzylic proton. Two signals at 3.51 and 3.02 ppm showed the two protons of $CH_2$. In the $^{13}C$ NMR spectrum, the main evidence was provided by the shifting of (C=O) peak from 168.48 ppm to (C=S) peak at 204.42 ppm which was also confirmed by a shift in absorption in the IR spectrum from 1705 $cm^{-1}$ to 1486 $cm^{-1}$.

Compound **286 b** & **c** gave spectroscopic data that similarly confirmed successful thionations.

### 2.3.1.1.3 Alkylation of 4-aryl-1-azetidine-2-thiones : Synthesis of 4-aryl-1-azetines

Thiolactams were converted to 1-azetines through alkylation with dimethyl sulfate or Meerwein's reagent (trimethyl or triethyl oxonium tetrafluoroborate). There are many alkylating reagents available but Meerwein's reagent was selected because of its good yields in *O*- or *S*-alkylations as well as its success in regioselective alkylation of similar β-lactams and β-thiolactams[157,161,191], whereby species such as β-lactams, β-thiolactams, thiocyanates and pyridine-2-one might undergo *N*-alkylation as well. Halides[192,193], diazomethane[194,195], diazoethane[196], tosylates[197] and dimethyl sulfate[198] are other commonly used alkylating reagents for such species.

In our strategy, dimethyl sulfate was used first for the alkylation of thiolactams but due to low yields this was not pursued with and alkylation of all thiolactams was performed with Meerwein's salts in dry DCM and worked up with potassium carbonate as a base to form imines. The volatility of these compounds and difficulty in isolation often resulted in low yields (Table 2.1), sometimes due to hydrolysis which reformed the original lactam.




**286** **287**

**Scheme 2.25**

| No | Product | Ar | R | % Yield |
|---|---|---|---|---|
| 1 | A | Phenyl | Me | 43 |
| 2 | B | Phenyl | Et | 54 |
| 3 | C | Tolyl | Me | 41 |
| 4 | D | Tolyl | Et | 38 |
| 5 | E | Naphthyl | Me | 40 |

**Table. 2.1** Substituents of 1-azetines **287**

2-Methylthio-4-phenyl-1-azetine **287a** was obtained as an orange oil in 43 % yield; the formation of imine was evidenced by appearance of a singlet at 2.48 ppm in the $^{1}$H NMR spectrum integrating for the three protons of the thiomethyl moiety, and the disappearance of the broad singlet of the amide at 8.28 ppm. A doublet of doublets at 5.25 with $J$ = 4.3 and 1.9 Hz confirmed the benzylic proton, and two signals at 3.56 and 2.95 ppm evidenced the two protons of the $CH_2$. The $^{13}$C NMR spectrum showed a peak at 11.51 ppm for SMe and a shift of the peak at 204.42 ppm (C=S) to 183.31 ppm (C=N), which was also confirmed by IR spectroscopy, where a shift in absorption from 1486 cm$^{-1}$ to 1655 cm$^{-1}$ confirmed the *S*-alkylation. MS data further confirmed the structure of compound **287a**.

Compound **287b** showed the expected spectroscopic characteristics. The IR spectrum of the compound showed no bands for the thioamide but instead showed a new peak at 1655 cm$^{-1}$

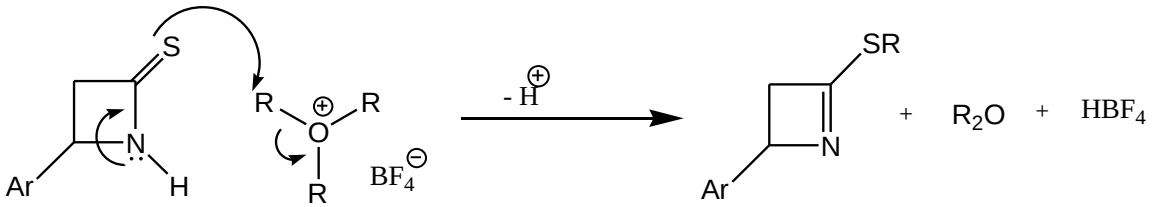
confirming (C=N). The $^{1}$H NMR spectrum showed the presence of ethyl group with a quartet at 3.06 ppm and a triplet at 1.40 ppm, with disappearance of the thioamide NH peak further confirming the S-alkylation. The loss of C=S peak in the $^{13}$C NMR spectrum and appearance of new quaternary carbon at 183.56 ppm confirmed that S-alkylation had occurred and not N-alkylation. High resolution mass spectroscopy data was also consistent with the assigned structure.

*S*-alkylation of 4-tolyl-1-azetidine-2-thione resulted in the synthesis of 2-methylthio-4-tolyl-1-azetine as an orange oil in 41 % yield. Spectroscopic analysis of the compound again confirmed the structure.

Compound **287d** yielded in 38 % as an orange oil, showed spectroscopic characteristics consistent with the assigned structure.

2-Methylthio-4-naphthyl-1-azetine was synthesized as an orange oil in 40 % yield. The evidence of the structure was provided by spectroscopic analysis. The main evidence was provided by the appearance of a singlet at 2.41 ppm in the $^{1}$H NMR spectrum for the three protons of the thiomethyl moiety and loss of the thioamide NH peak at 7.34 ppm. The presence of the ring was confirmed by a doublet of doublets at 5.07 ppm showing the benzylic proton and two more doublets of doublets at 3.51 and 2.94 ppm confirming the presence of the two protons of the $CH_2$. The $^{13}$C NMR spectrum provided further evidence of S-alkylation with a peak at 183.35 ppm for C=N and loss of the C=S signal from 204.41 ppm, whilst the IR spectrum showed a peak at 1609 cm$^{-1}$ confirming the S-alkylation as a result of the formation of the 1-azetine. HRMS data was also consistent with the assigned structure.

Synthesis of the 1-azetines proceeds through the following proposed mechanism:

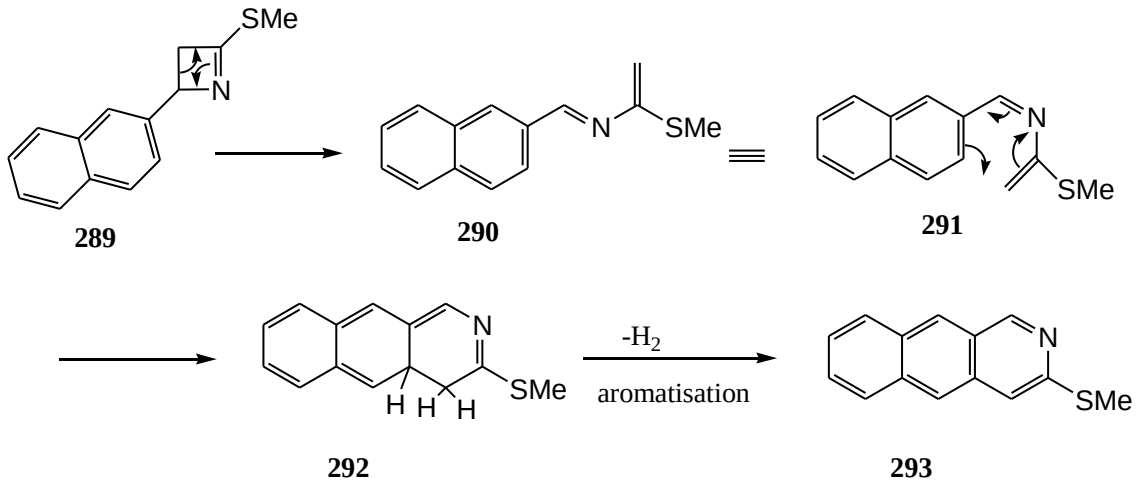



**286** **288** **287**

**Scheme 2.26**

It was observed that 2-methylthio-4-naphthyl-1-azetine was unstable at room temperature and underwent quantitative conversion to 2-methylthio-benzoquinoline after 24 hours. The structure was assigned to the product after spectroscopic analysis. $^{1}$H NMR spectrum showed one singlet at 2.83 ppm confirming the presence of the thiomethyl moiety with the rest of the signals showing as eight aromatic protons indicating the emergence of a new aromatic ring. This was further confirmed by loss of the three doublets of doublets at 5.07, 3.51 and 2.94 ppm, respectively. The $^{13}$C NMR spectrum showed one signal at 13.26 ppm for thiomethyl group, together with five quaternary carbons and eight CH signals between 120.87 and 158.51 which confirmed the presence of three aromatic rings and the loss of the four membered ring of the azetine. HRMS data was also consistent with the assigned structure. It showed a mass of 226.0684 for a calculated mass of 226.0692 confirming the product as 2-methylbenzoquinoline, a process that involves loss of two hydrogen atoms.

It is proposed that a [2 +2] ring opening occurred to form a vinylic imine which undergoes an intramolecular rearrangement and aromatisation via loss of hydrogen to form the benzoquinoline. Other examples of this type of rearrangement have recently been observed by other workers in the group, but this is the only example observed in this work.

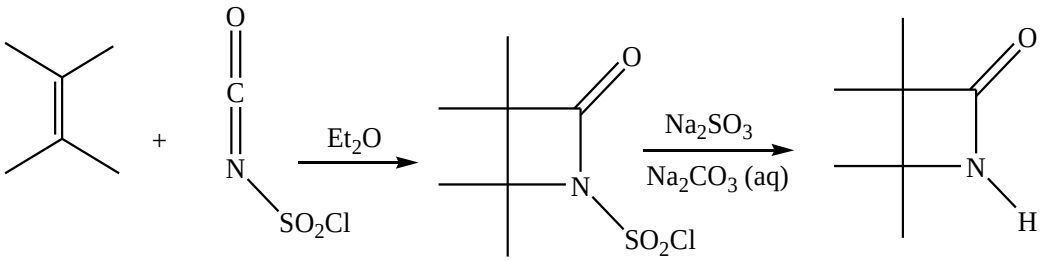



**Scheme 2.27**

## 2.3.1.2 Synthesis of 3,3,4,4-tetramethyl-1-azetines

### 2.3.1.2.1 Synthesis of 3,3,4,4-tetramethyl-1-azetidine-2-one

The same protocol was followed as above. Thus, the β-lactam ring was formed as a result of [2+2]-cycloaddition of 2,3-dimethylbut-2-ene with chlorosulfonyl isocyanate after which reduction with sodium sulfite and sodium carbonate afforded the β-lactam in 71 % yield.

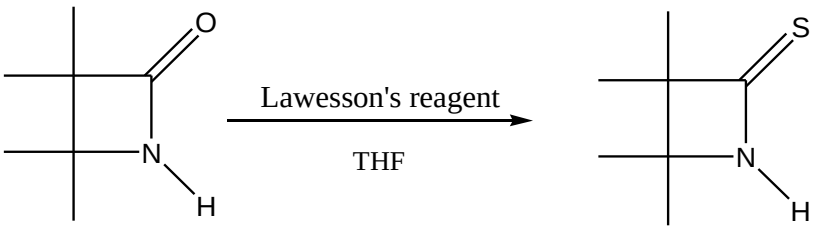



**294** **283** **295** **296**

**Scheme 2.28**

### 2.3.1.2.2 Synthesis of 3,3,4,4-tetramethyl-1-azetidine-2-thione

Thionation of β-lactam was conducted with Lawesson's reagent in dry THF to yield a white solid in 47 % as the thiolactam. The reaction proceeded with the same mechanism as described before.




**296** **297**

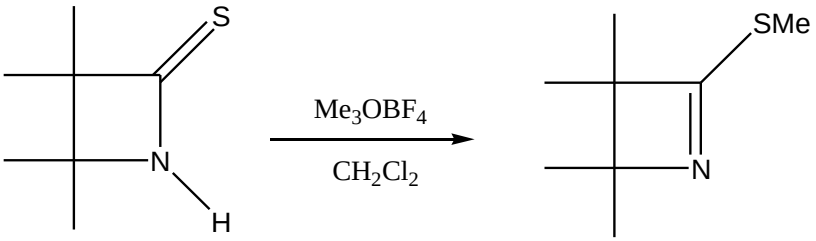
**Scheme 2.29**

The evidence of thionation was provided by IR spectroscopy with a shift in absorption from 1703 $cm^{-1}$ (C=O) to 1492 $cm^{-1}$ (C=S) and was also confirmed by $^{13}C$ NMR spectroscopy with a peak at 212.27 ppm for C=S and loss of the C=O peak from 174.91 ppm. $^{1}H$ NMR

spectroscopy also showed a shift in NH peak from 6.02 to 8.23 ppm, a feature seen in all of the thionations reported above.

### 2.3.1.2.3 Synthesis of 2-methylthio-3,3,4,4-tetramethyl-1-azetine

Conversion of the thiolactam to the 1-azetine was performed by S-alkylation by using Meerwein's reagent as described before to get 2-methylthio-3,3,4,4-tetramethyl-1-azetine as a yellow oil in 31 % yield. Due to volatility and instability it proved hard to achieve a better yield. The structure of the compound was confirmed with NMR spectroscopy.



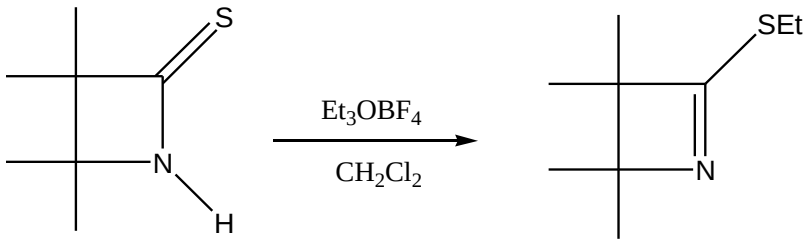

**297** **298**

**Scheme 2.30**

The $^{1}H$ NMR spectrum showed three singlets altogether in a ratio of 2:2:1 confirming the five methyl groups of the compound. Two singlets at 1.26 and 1.12 ppm respectively integrated for six protons confirming two sets of methyl groups while a third singlet at 1.97 ppm evidenced the SMe confirming the *S*-alkylation of the azetidine-thione. The $^{13}C$ NMR spectrum further provided evidence for azetine formation with a peak at 182.96 ppm for C=N and with the loss of the C=S peak from 212.27 ppm. Two quaternary carbons at 69.82 ppm and 51.34 ppm confirmed the presence of the remaining carbons.

### 2.3.1.2.4 Synthesis of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine

Meerwein's reagent was used to form 2-ethylthio-3,3,4,4-tetramethyl-1-azetine in 30 % yield as a yellow oil.



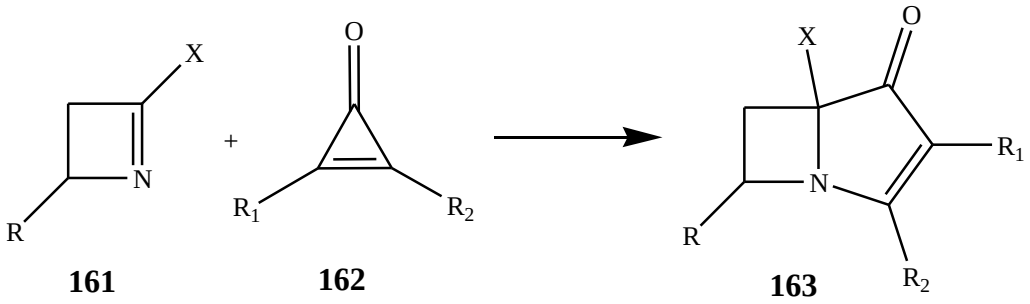

**297** **299**

**Scheme 2.31**

Spectroscopic analysis confirmed the structure, with the presence of ethyl group evidenced by a quartet at 2.96 and a triplet at 1.33 ppm in the $^{1}H$ NMR spectrum. Four methyl groups were confirmed by two singlets at 1.25 ppm and 1.13 ppm. The structure was further confirmed by the $^{13}C$ NMR spectrum with a shift in peak from 212.29 to 186.96 ppm establishing that it was *S*-alkylation and not *N*-alkylation.

## 2.3.2 Reactivity of 1-azetines with cyclopropenones

Based on the known reactivity of electron rich imines with cyclopropenones[157,159,160], it was envisaged that the reaction of 1-azetines with cyclopropenones will give bicyclic compounds with the structure shown below. Such bicyclic systems might produce interesting results upon heating.



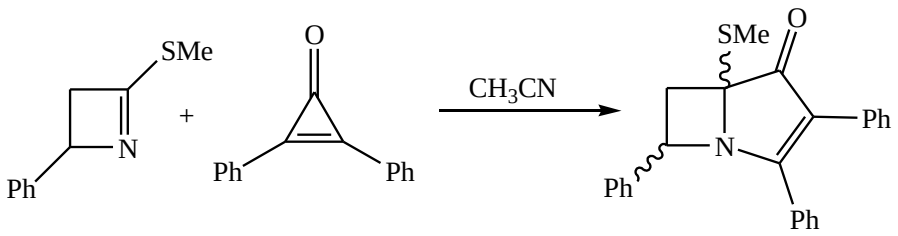

**161** **162** **163**

**Scheme 2.32**

The chemistry and applications of cyclopropenones [199-201] and their acetals/ketals [202-204] has gained momentum in recent years and there have been several other reports of imines reacting with cyclopropenones[157,159,205-208]. The topic of 3-carbon 1,3-dipole equivalents is itself an important area due to the potential of such processes to provide access to 5-

membered rings in [3+2]-cycloaddition reactions[209-215], and it should be noted that the cyclopropenone is acting as an all-carbon 1,3-dipole equivalent in this reaction.

The reaction of 2-methylthio-4-phenyl-1-azetine with diphenylcyclopropenone afforded the *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **301** as a yellow oil in 59 % yield as a mixture of diastereoisomers in a 4/5 ratio.



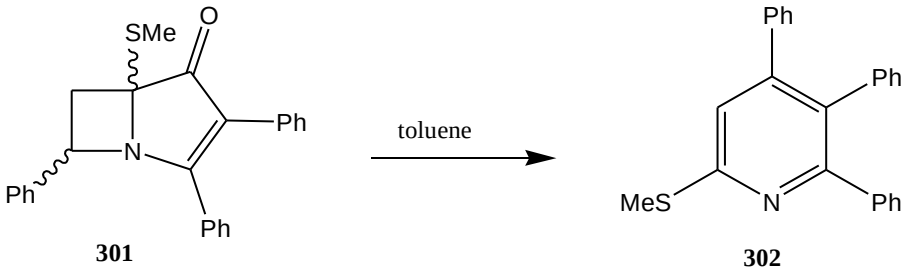

**287a** **300** **301**

**Scheme 2.33**

Spectroscopic analysis confirmed the structure of the product. The $^{1}H$ NMR spectrum confirmed fifteen aromatic protons in the range of 6.81-7.51 ppm as a series of multiplets. All three protons of the four-membered ring appeared as two sets of signals showing the product as a mixture of diastereoisomers. Two sets of doublets of doublets at 5.58 and 4.25 ppm ($J$ = 8.1, 8.1 and 5.5, 9.6 Hz), respectively, confirmed the benzylic CH protons. The two protons of the $CH_2$ appeared as four sets of doublets of doublets confirming the product as a mixture of diastereoisomers. One set of doublet of doublets appeared at 3.18 and 2.50 ppm ($J$ = 9.6, 12.6 and 5.5, 12.9 Hz) for one proton of $CH_2$, whereas another set of doublet of doublets appeared at 2.97 and 3.03 ($J$ = 8.1, 12.9 and 8.1, 12.6 Hz) to confirm the second proton of $CH_2$. Two peaks at 2.14 and 2.08 evidenced the thiomethyl moiety and further indicated that the formation of the product occurred as a diastereomeric mixture.

The $^{13}C$ NMR spectrum further confirmed the formation of two diasteroisomers by showing double signals. For example, the signals for carbonyl appeared at 202.89 and 202.56 ppm. The unsaturated carbons of the enone appeared at 177.64 and 175.38 and at 126.33 and 124.03 ppm. The benzylic CH of the ring appeared at 66.63 and 66.16 ppm, and the $CH_2$ of the ring appeared at 31.29 and 29.90; the carbon of the thiomethyl was found at 11.92 and 11.69 ppm.

In the next step, the reactivity of *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* was investigated by heating it in boiling toluene. This resulted in the complete consumption of the starting material and formation of a new product identified as a tetrasubstituted pyridine as the only product, formed in 71 % yield as white crystals.

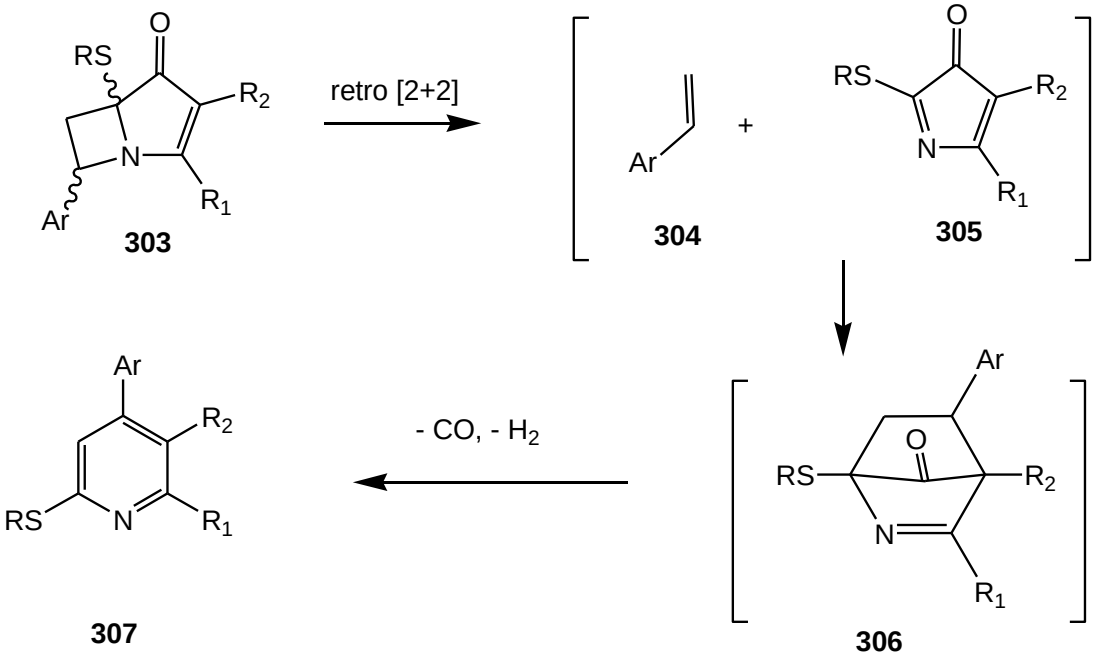



**301** **302**

**Scheme 2.34**

Spectroscopic analysis was performed to assign a structure to the product. The $^{1}H$ NMR spectrum showed a singlet at 2.7 ppm integrating to three protons indicating the presence of the thiomethyl group; the rest of signals were in the aromatic region only. There were no signals to indicate the presence of the four membered ring which means loss of the four membered ring of the bicyclic adduct has occurred. In the aromatic region, signals ranging from 6.87 to 7.35 ppm confirmed the presence of sixteen protons which indicates the presence of three phenyl groups and one more proton which appeared as a singlet at 7.23 ppm confirming that it could belong to the pyridine ring. The formation of the pyridine ring was further evidenced by the $^{13}C$ NMR spectrum showing the loss of carbonyl group from 202.89 and 202.56 ppm, and loss of the carbon peaks of the four-membered ring. The presence of ten CH peaks and seven quaternary carbons in the aromatic region indicated that three phenyl groups are substituted to a tetrasubstituted pyridine ring; the fourth substituent is SMe which appeared at 13.39 ppm in $^{13}C$ NMR spectrum. IR spectroscopy and HRMS further confirmed the structure of the product as *2,3,4-triphenyl-6-methylthio-1-pyridine*.

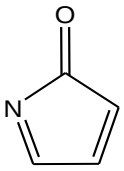
After the characterization of the product as a tetrasubstituted pyridine and keeping in mind the structure of the starting material, it is suggested that formation of this pyridine occurred through the reaction mechanism shown below.




**Scheme 2.35**

The first step of the suggested mechanism involves [2+2] cycloreversion of the bicyclic compound **303** to generate a styrene and an intermediate azacyclopentadienone **305**. These two species then undergo a regioselective [4+2] cycloaddition to form the intermediate **306**. Chelotropic extrusion of carbon monoxide and aromatization by loss of hydrogen results in the synthesis of the pyridine, as shown in scheme 2.35.

The synthesis of the pyridine through this mechanism is equivalent to a well known process [216-221] by which the corresponding all carbon diene, cyclopentadienone, is used to access the benzene ring. The azacyclopentadienone ring is rare due to the difficulties in accessing this elusive system in a stable form, but its formation and use are known [222-225]. Of particular relevance to our work is specie **308.**




**308**

**Fig. 2.4**

This has been generated from a polymeric 5-sulfonate of 3-pyrrolin-2-one and shown to act as a diene toward a polymer supported alkyne, allowing access to one example of a pyridine ring[226].

Based upon the result shown in scheme 2.35 with compound **303a** with compound **301**, it was decided to explore this reaction fully. This necessitated the syntheses of some other azabicyclo[3.2.0]hept-2-en-4-ones **303b-g** to act as potential pyridine precursors. For this the series of 1-azetines **287a-e** discussed above were reacted smoothly with cyclopropenones to give the azabicyclo[3.2.0]hept-2-en-4-ones **303b-g** as shown in Table 2.2 below. These were found to be unstable mixtures of diastereoisomers, which were made and used within 24 hours.

| Entry | Product (**303)** | Ar | R | $R^1$ | $R^2$ | % yield (**303)** |
|---|---|---|---|---|---|---|
| 1 | **a** | Ph | Me | Ph | Ph | 62 |
| 2 | **b** | Ph | Et | Ph | Ph | 63 |
| 3 | **c** | Ph | Me | H | Ph | 52 |
| 4 | **d** | 4-Tol | Me | Ph | Ph | 63 |
| 5 | **e** | 4-Tol | Et | Ph | Ph | 66 |
| 6 | **f** | 2-Naphth | Me | Ph | Ph | 51 |
| 7 | **g** | Ph | Et | n-Bu | n-Bu | 58 |

**Table 2.2.** Synthesis of azabicyclo[3.2.0]hept-2-en-4-ones **303**.

Diphenylcyclopropenone was commercially available, phenylcyclopropenone was synthesized by another worker in the group by the cyclization of 1-bromo-3-chloro-3-phenyl acetone acetal[227] and dibutylcyclopropenone was synthesized from the reaction of dichlorocarbene with 5-decyne and subsequent hydrolysis[228]. Each of the azabicyclo[3.2.0]hept-2-en-4-ones **303b-g** gave the desired pyridines **307b-g** when heated in xylene or toluene, as shown in the table below, in good to reasonable yields.

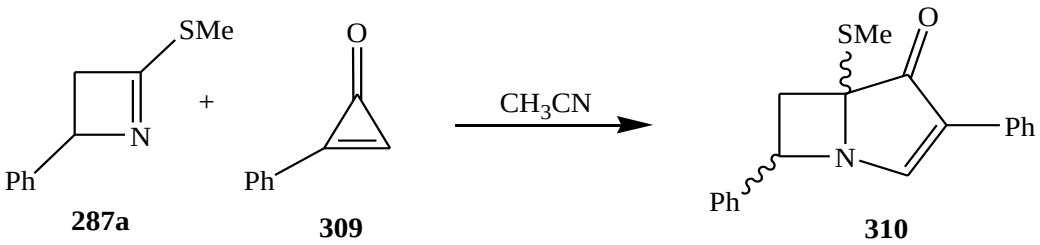
| Entry | Pyridine (**307**) | Ar | R | $R^1$ | $R^2$ | % yield (**307**) |
|---|---|---|---|---|---|---|
| 1 | **a** | Ph | Me | Ph | Ph | 71 |
| 2 | **b** | Ph | Et | Ph | Ph | 75 |
| 3 | **c** | Ph | Me | H | Ph | 62 |
| 4 | **d** | 4-Tol | Me | Ph | Ph | 79 |
| 5 | **e** | 4-Tol | Et | Ph | Ph | 72 |
| 6 | **f** | 2-Naphth | Me | Ph | Ph | 69 |
| 7 | **g** | Ph | Et | n-Bu | n-Bu | 73 |

**Table 2.3.** Synthesis of pyridines **307a-g** from azabicyclo[3.2.0]hept-2-en-4-ones **303a-g**.

The synthesis of these azabicyclo[3.2.0]hept-2-en-4-ones and subsequent conversion into pyridines will be discussed in detail below.

### 2.3.2.1 Synthesis and reactivity of 5-methylthio-3,7-diphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one.

2-Methylthio-4-phenyl-1-azetine was reacted with phenylcyclopropenone, which was synthesized in the group using the method described above[227], to give *5-methylthio-3,7-diphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* in 52 % yield as a yellow oil and as a mixture of diastereoisomers in a ~5/6 ratio. Phenylcyclopropenone gave only the *3-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* regioisomer, possibly due to the 1-azetine attacking the least hindered cyclopropenone carbon.



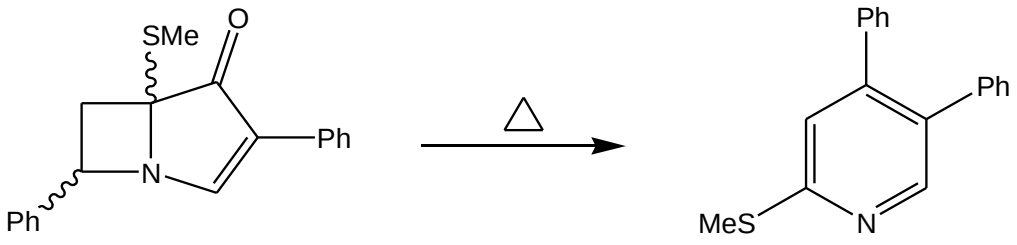

**287a** **309** **310**

**Scheme 2.36**

The spectroscopic analysis allowed us to assign a structure to the product. $^{1}$H NMR showed two singlets at 8.36 and 7.76 ppm to confirm the presence of the alkene proton of the five membered ring. Ten aromatic protons in the range of 7.26-7.85 ppm as a series of multiplets evidenced the presence of two phenyl groups. All three protons of the four-membered ring appeared as two sets of signals confirming that the product was a mixture of diastereoisomers. Two sets of doublet of doublets at 5.66 and 4.65 ppm with coupling constants $J$ = 7.6, 9.6 and 5.2, 10.5 Hz, respectively, are consistent with a benzylic CH proton. The two protons of the $CH_2$ of the ring appeared as four sets of doublets of doublets as expected for a mixture of diastereoisomers. One set of these doublets of doublets appeared at 3.06 and 3.00 ppm ($J$ = 9.6, 12.6 and 9.6, 12.4 Hz) for one proton of $CH_2$, whereas another set appeared at 2.83 and 2.48 ppm ($J$ = 7.6, 12.4 and 5.2, 12.6 Hz). Two peaks at 2.04 and 2.03 for the thiomethyl moiety completed the assignment of the $^{1}$H NMR spectrum.

The structure of the product was further confirmed with a $^{13}$C NMR spectrum which showed double signals for the carbons as expected with two diasteroisomers. Signals for the carbonyl appeared at 203.13 and 201.74 ppm whereas peaks for the carbons of the alkene appeared at 177.64, 175.38 and 126.33, 124.03 ppm, respectively. Double peaks for the four membered ring carbons and thiomethyl moiety completed a consistent assignment. The regiochemistry of the product was confirmed with the help of HMBC spectrum, which showed a clear CH to CH cross peak.

Keeping in mind the successful thermolysis (scheme 2.35) of the azabicyclic adduct **303** to produce the pyridine **307**, azabicyclic compound **310** was also treated with boiling toluene until disappearance of starting material. The process again afforded the pyridine **311**, on this occasion as white crystals in 62 % yield, shown in scheme 2.37.




**310** **311**

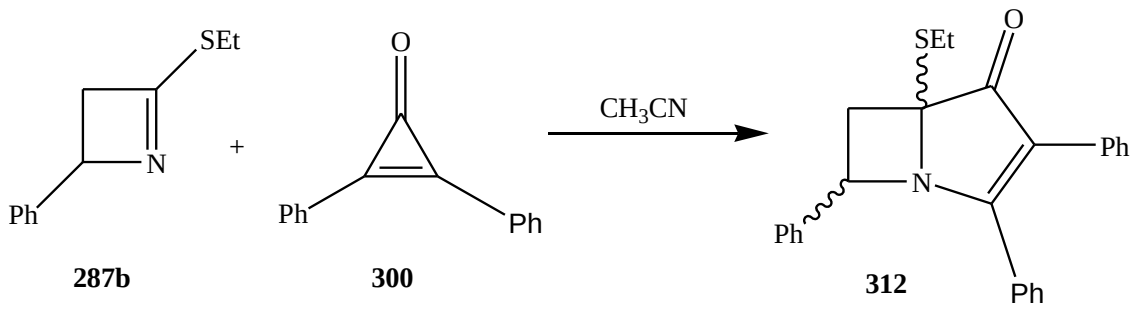
**Scheme 2.37**

Spectroscopic analysis provided the evidence for the structure of the product. The IR spectrum showed no carbonyl to be present. In the $^{1}H$ NMR spectrum a singlet at 8.1 ppm showed one proton of the pyridine ring, whereas two multiplets between 7.31-7.12 evidenced eleven protons confirming two phenyl groups and one more proton of the pyridine ring. There were no signals to indicate the presence of the four membered ring confirming its loss. A peak at 2.68 ppm confirmed the presence of SMe. Pyridine ring formation was further evidenced by $^{13}C$ NMR spectrum showing the loss of carbonyl group from 203.13 and 201.74 ppm (compound **310** was a mixture of diastereoisomers), and loss of the carbon peaks of the four-membered ring. The presence of eight CH peaks and five quaternary carbons in the aromatic region was consistent with two phenyl groups substituted to the pyridine ring. The methyl of the third substituent SMe appeared at 13.48 ppm.

HRMS further confirmed the structure of the product as *3,4-diphenyl-6-methylthio-1-pyridine* with a mass of 278.1000 for a required mass of 278.0998.

## 2.3.2.2 Synthesis of other pyridines.

With two successful examples demonstrated, it was the next task to show that a series of azabicyclo[3.2.0]hept-2-en-4-ones could be made and converted into pyridines. Diphenylcyclopropenone was reacted with 2-ethylthio-4-phenyl-1-azetine in acetonitrile at room temperature to afford *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* as a yellow oil in 61 % yield as a mixture of diastereoisomers in a 3:5 ratio.



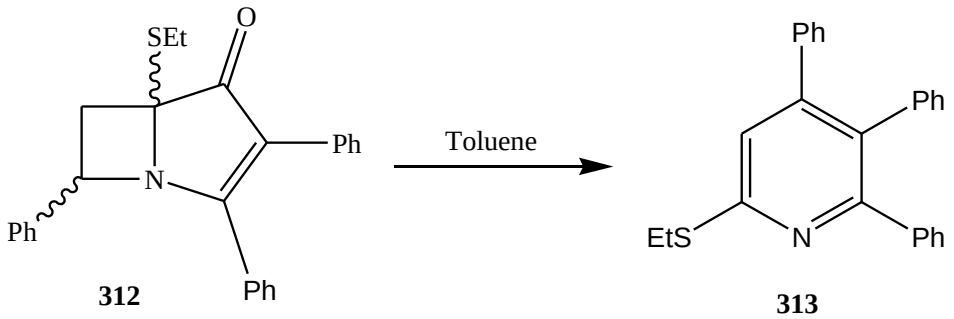

**287b** **300** **312**

**Scheme 2.38**

The structure of the product **312** was confirmed by spectroscopic analysis. $^{1}$H NMR confirmed all three protons of the four-membered ring which appeared as two sets of signals showing the product to be a mixture of diastereoisomers. Two sets of doublet of doublets at 5.60 and 4.28 ppm ($J$ = 8.3, 8.3 and 5.5, 9.6 Hz) respectively confirmed the benzylic CH protons. The two protons of the $CH_2$ of the ring appeared as doublets of doublets and multiplets confirming the product was a mixture of diastereoisomers. Two triplets between 1.30-1.23 ppm (2 x diastereo, 3H, t, $J$ = 7.2 Hz) evidenced the thioethyl moiety with the $CH_2$ of the SEt appearing at ~ 3.0 and ~ 2.6 ppm as complex multiplets. Fifteen aromatic protons in the range of 6.81-7.51 ppm as a series of multiplets confirmed the presence of three phenyl groups.

The $^{13}$C NMR spectrum confirmed the presence of two diasteroisomers by showing double signals in all cases. For example, the signals for carbonyl appeared at 202.86 and 202.46 ppm. The unsaturated carbon of the enone β position appeared at 176.99 and 174.85 ppm whereas the α carbon of the enone appeared at 126.14 and 123.79 ppm. The benzylic CH of the ring appeared at 66.62 and 65.98 ppm, whilst the $CH_2$ of the ring appeared at 35.14 and 31.86 ppm, and the carbons of thioethyl group were found at 23.70, 23.59, 14.59 and 14.24 ppm.

The reactivity of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **312** was investigated by heating it in toluene until the complete consumption of the starting material was observed by TLC. The formation of the *2,3,4-triphenyl-6-ethylthio-1-pyridine* **313** was observed as the only product in 75 % yield, isolated as white crystals after chromatography, when the bicyclic precursor was heated overnight in toluene.




**312** **313**

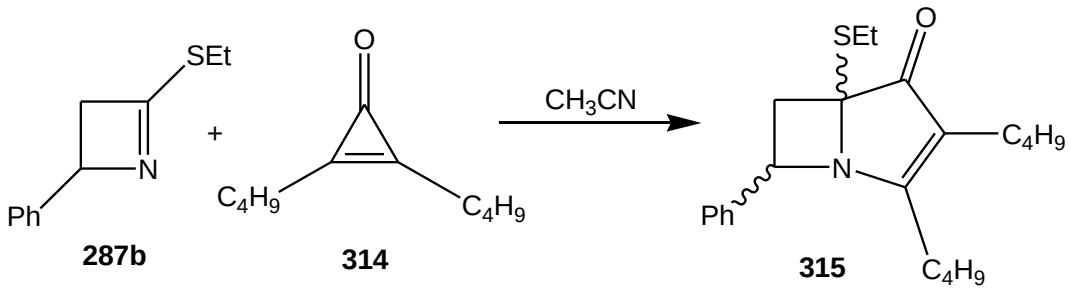
**Scheme 2.39**

The structure of the product was assigned as a result of spectroscopic analysis which confirmed the synthesis of a pyridine with three phenyl groups and one thioethyl group as

substituents. Different signals ranging from 6.91 to 7.34 ppm in the $^{1}H$ NMR spectrum confirmed the presence of sixteen protons which indicates the presence of three phenyl groups and one more proton that belongs to the pyridine ring. A quartet at 3.32 and triplet at 1.51 ppm with coupling constant of 7.3 Hz evidenced the presence of the thioethyl moiety. There were no signals to indicate the presence of a four-member ring which confirms its loss. The formation of the pyridine ring was further evidenced by $^{13}C$ NMR spectrum showing the loss of carbonyl group from 202.86 and 202.46 ppm, and loss of carbon peaks characteristic of the four-member ring. The presence of ten CH peaks and seven quaternary carbons in the aromatic region was consistent with three phenyl groups substituted on the pyridine ring, whereas the fourth substituent is SEt which shows signals at 24.52 and 15.00 ppm, respectively, for the $CH_2$ and $CH_3$ group.

IR and HRMS further confirmed the structure of the product as *2,3,4-triphenyl-6-ethylthio-1-pyridine*, with IR showing loss of the carbonyl group and HRMS showing the mass (m/z) of 368.1460 for a required mass of 368.1467.

It was next decided to try a dialkylcyclopropenone to investigate the reactivity of 1-azetines with dialkylcyclopropenones. For this purpose, we selected dibutylcyclopropenone, which had been synthesized elsewhere in the group by reacting dichlorocarbene with 5-decyne and subsequent hydrolysis[228]. Reaction of dibutylcyclopropenone with 2-ethylthio-4-phenyl-1-azetine (Scheme 2.40) afforded *5-ethylthio-2,3-dibutyl-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **315** as a dark yellow oil in 58 % yield as a mixture of diastereoisomers in a 1/1.5 ratio.



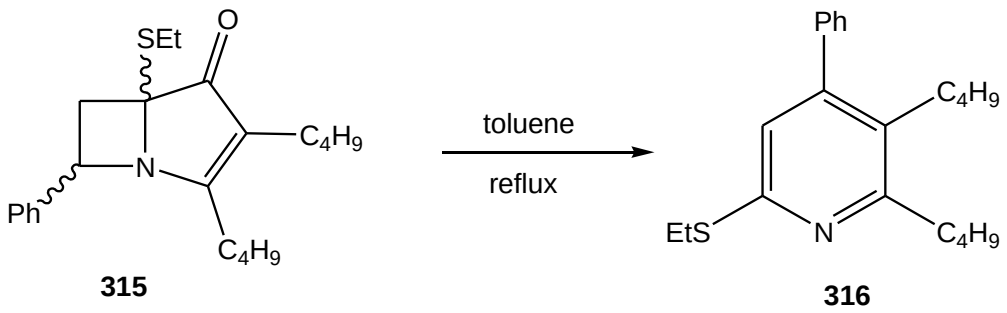

**Scheme 2.40**

The spectroscopic analysis provided the evidence for the structure of the product. The phenyl group was confirmed with three different signals integrating for five protons in the aromatic

region on the $^{1}H$ NMR spectrum. The three protons of the four-membered ring appeared as the characteristic two sets of signals showing the product as a mixture of diastereoisomers, with, for example two sets of doublet of doublets at 5.48 and 4.30 ppm ($J$ = 8.5, 8.5 and 5.4, 8.7 Hz) for the benzylic CH proton. The twelve protons of the alkyl $CH_2$ groups and the two protons of the thioethyl group appeared in a series of multiplets. Two triplets between 1.17-1.21 with coupling constant of $J$ = 7.4 Hz, confirmed the $CH_3$ of thioethyl moiety, and four triplets 0.94-0.77 ppm evidenced the presence of two $CH_3$ of alkyl chains in a mixture of diastereoisomers.

It was further confirmed with $^{13}C$ NMR spectroscopy that the bicyclic adduct was formed as a diasteromeric mixture with the characteristic doubling of each carbon signal. For example, the signals for the carbonyl appeared at 205.44 and 204.96 ppm. The signals for unsaturated β-carbon of the enone appeared at 182.78 and 180.98 ppm whereas, the α carbon of the enone appeared at 126.22 and 127.26 ppm. The $CH_2$ of the four-membered ring appeared at 64.98 and 64.58 whereas the benzylic CH of the ring appeared at 75.45 and 75.11 ppm. Fourteen $CH_2$ and six $CH_3$ peaks confirmed the diastereomeric mixture of the desired product.

The treatment of *5-ethylthio-2,3-dibutyl-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **315** in boiling toluene afforded *2,3-dibutyl-4-phenyl-6-ethylthio-1-pyridine* **316** as the only product in 73 % yield as a clear oil after full consumption of starting material.




**315** **316**

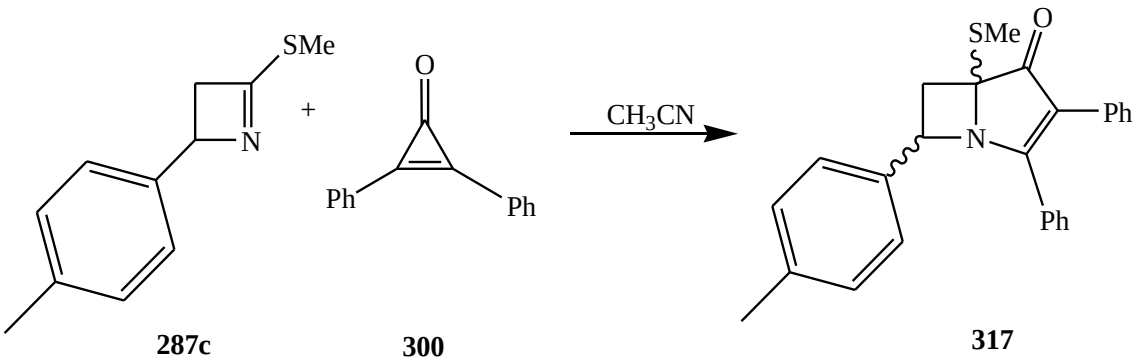
**Scheme 2.41**

Spectroscopic analysis was used to assign a structure to the product. The $^{1}H$ NMR spectrum confirmed the presence of one phenyl group and one proton of the pyridine ring which appeared as a singlet at 6.84 ppm. Eighteen protons of two alkyl chains confirmed the two butyl groups. A quartet at 3.2 and triplet at 1.4 ppm with coupling constant of 7.3 Hz

evidenced the presence of thioethyl moiety. Furthermore, there were no signals to indicate the presence of the four-membered ring which confirms its loss. IR spectroscopic analysis confirmed the loss of carbonyl group. The $^{13}C$ NMR spectrum showed the loss of the carbonyl group from 202.86 and 202.46 ppm and loss of the carbon peaks of the four-membered ring. The presence of seven $CH_2$ and three methyl peaks confirmed the presence of the two butyl chains and thioethyl moiety.

HRMS further confirmed the structure of the product as *2,3-dibutyl-4-phenyl-6-methylthio-1-pyridine* **316**, by showing the mass (m/z) of 328.2086 for a required mass of 328.2093.

With the ability of different cyclopropenones to give adducts, and then pyridines, from 4-phenyl-2-thioalkyl-1-azetines established, it was next decided to look at some other 4-aryl-2-thioalkyl-1-azetines. Thus, the reaction of 2-methylthio-4-tolyl-1-azetine with diphenylcyclopropenone afforded *5-methylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **317** as a yellow oil in 63 % yield as a mixture of diastereoisomers in a 1/1.5 ratio, as shown in Scheme 2.42.




**287c** **300** **317**

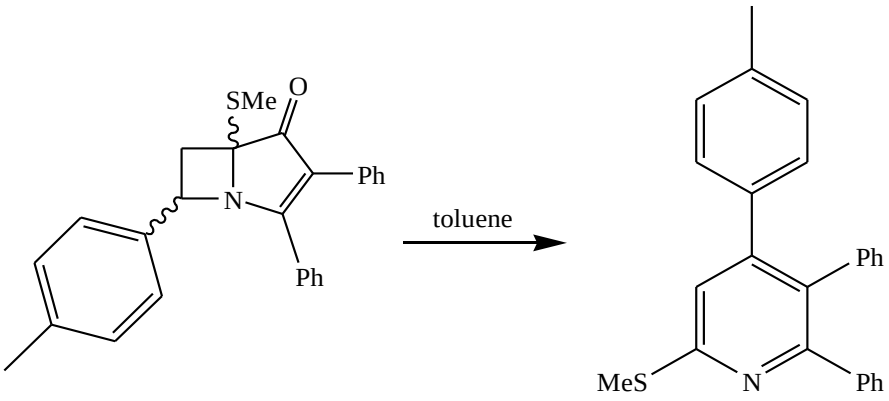
**Scheme 2.42**

Spectroscopic analysis again confirmed the structure of the product as a mixture of diastereoisomers. The $^1H$ NMR spectrum confirmed ten aromatic protons for the two phenyl rings in the range of 7.12-7.53 ppm as a series of multiplets. The four aromatic protons of the tolyl group appeared as four doublets between 7.25-6.75 ppm consistent with the diastereomeric mixture. All three protons of the four-membered ring appeared as two sets of signals further showing the product was a mixture of diastereoisomers. Thus, two sets of doublet of doublets at 5.54 and 4.27 ppm were seen for the benzylic CH protons. The two protons of the $CH_2$ of the ring appeared as four sets of doublets of doublets with one set at

3.16 and 2.49 ppm (2 x diastereo, 1H, *J* = 9.6, 12.8 and 5.1, 12.8 Hz) and another set of doublet of doublets at 2.95 and 3.02 ppm (2 x diastereo, 1H, *J* = 8.1, 12.8 and 8.5, 12.8 Hz). Four singlets between 2.41-2.07 ppm evidenced the ArMe and SMe moieties, and confirm the formation of the product as a diastereomeric mixture.

The $^{13}C$ NMR spectrum showed the characteristic double signals for each carbon. For example, the signals for the carbonyl appeared at 202.83 and 202.46 ppm. The β-carbon of the enone was at 177.56 and 177.52 whereas, the α-carbon of the enone appeared at 126.21 and 123.75 ppm. Peaks at 66.38 and 65.92 ppm were seen for the benzylic CH of the ring whereas the $CH_2$ of the ring appeared at 34.35 and 31.01 ppm. Four methyl signals for the ArMe and SMe further confirmed the product as a diastereomeric mixture.

The reactivity of *5-methylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **317** was investigated by heating it in boiling toluene which resulted in the complete consumption of the starting material and formation of the tetrasubstituted pyridine **318** as the only product in 74 % yield as white crystals, as shown in Scheme 2.43.




**317** **318**

**Scheme 2.43**

Spectroscopic analysis was performed to assign a structure to the product. The $^{1}H$ NMR spectrum showed the four aromatic protons of the tolyl group as the characteristic two doublets at 7.02 and 6.96 ppm respectively with coupling constants of *J* = 8.1 Hz for each. Eleven more aromatic protons between 7.34-6.88 confirmed the presence of two phenyl groups and one proton of the pyridine ring. Two singlets at 2.68 and 2.31 ppm integrating for three protons each confirmed the SMe and ArMe respectively.

The $^{13}C$ NMR spectrum showed the loss of carbonyl signals from 202.83 and 202.46 ppm, and loss of the carbon peaks of the four-membered ring. The presence of nine CH signals and

eight quaternary carbons in the aromatic region indicated that three aryl groups were substituted on the pyridine ring whereas the fourth substituent is SMe which appeared at 13.42 ppm. A peak at 21.18 ppm confirmed the presence of ArMe.

HRMS showed the mass (m/z) of 368.1468 required for 368.1467. On this occasion, the use of the tolyl group allowed us to confirm the regiochemistry of the product with X-ray crystallographic studies, which showed the structure with two phenyl groups at positions 2 and 3 of the pyridine, the tolyl group at position 4 and the thiomethyl at the 6 position. (Crystallographic data have been deposited at the Cambridge Crystallographic data Centre as a CIF deposit with file number 847593. Copies of these data can be obtained free of charge on application to CCDC, email deposit@ccdc.cam.ac.uk.).

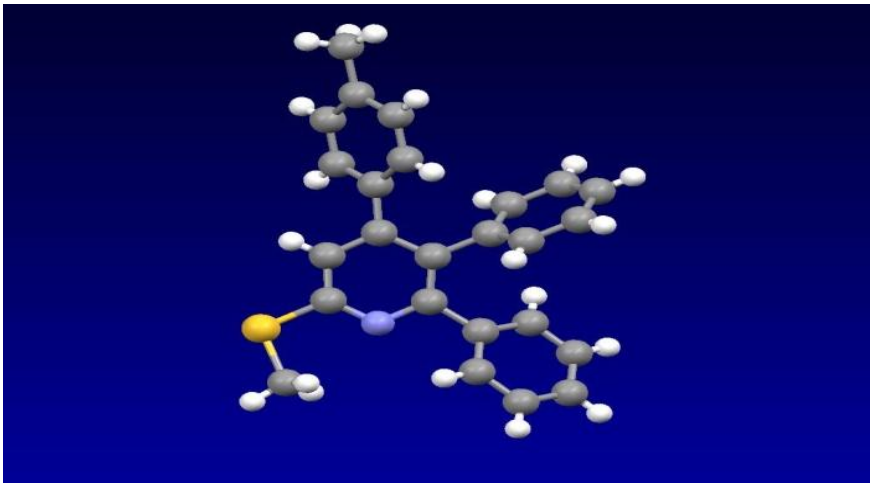
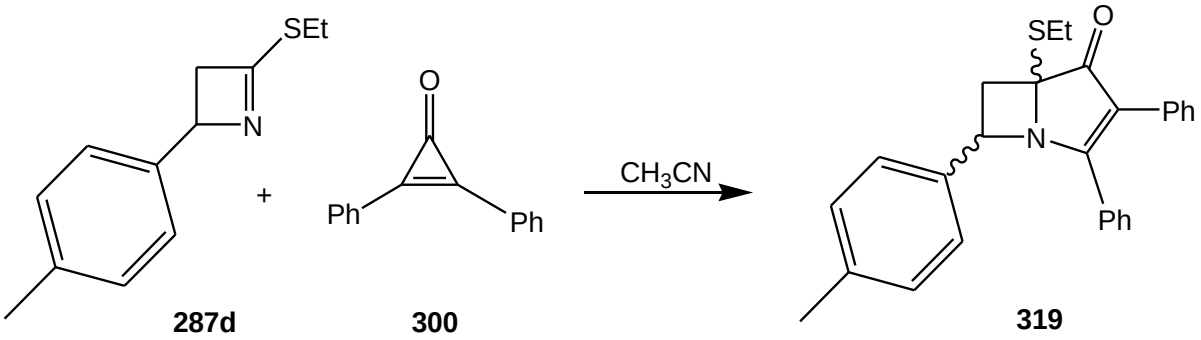


**Fig. 2.5** *2,3-diphenyl-4-tolyl-6-methylthio-1-pyridine* **318.**

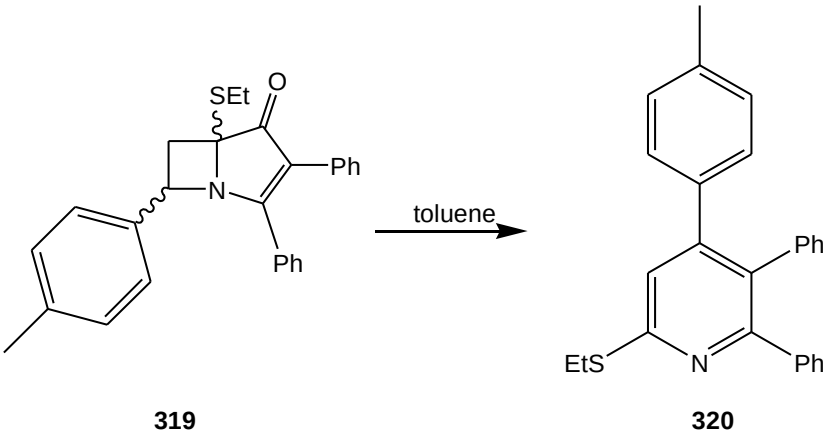
Diphenylcyclopropenone was also reacted with 2-ethylthio-4-tolyl-1-azetine to afford *5-ethylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **319** as a yellow oil in 66 % yield as a mixture of diastereoisomers in a 1/1.5 ratio. The product had fully consistent $^{1}H$ and $^{13}C$ spectra which were very similar to those discussed above for the SMe compound.




**Scheme 2.44**

In the $^{1}$H NMR spectrum a multiplet between 2.70-2.47 ppm and two triplets at 1.30 and 1.28 ppm with coupling constant $J$ = 7.3 Hz evidenced the additional presence of the thioethyl belonging to each diastereoisomer. The $^{13}$C NMR spectrum showed the signals of the thioethyl group at 23.70, 23.57, 14.63 and 14.60 ppm.

As expected, *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **319** gave *2,3-diphenyl-4-tolyl-6-ethylthio-1-pyridine* **320** when heated overnight in toluene. The product was isolated in 75 % as a white crystalline solid after chromatographic purification.



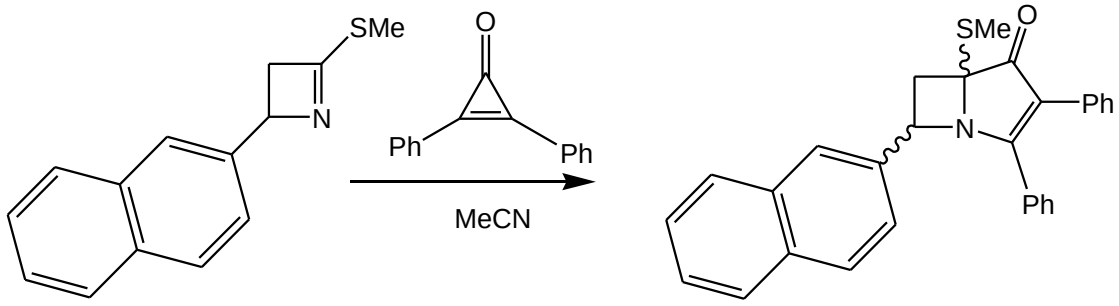

**Scheme 2.45**

The $^{1}$H NMR spectrum confirmed the presence of fifteen aromatic protons which indicates the presence of the three aryl groups and the pyridine ring. The four aromatic protons of the tolyl moiety were evidenced by two doublets at 7.02 and 6.97 ppm with coupling constants $J$ = 8.2 Hz each. A quartet at 3.32 and triplet at 1.51 ppm both with coupling constants of 7.3 Hz evidenced the presence of the thioethyl moiety. The $^{13}$C NMR spectrum showed the loss

of the carbonyl group, confirmed by IR as well as loss of the carbon peaks of the four-membered ring. The presence of nine CH peaks and eight quaternary carbons in the aromatic region indicated that two phenyl and one tolyl groups are substituted to the pyridine. The fourth substituent this time is SEt which appeared at 24.52 ($CH_2$) and 14.99 ($CH_3$) ppm.

HRMS further confirmed the structure of the product as *2,3-diphenyl-4-tolyl-6-ethylthio-1-pyridine* by showing the mass (m/z) of 382.1624 for a required mass of 382.1624.

2-Methylthio-4-naphthyl-1-azetine was also reacted with diphenylcyclopropenone to afford *5-methylthio-2,3-diphenyl-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **321** in 51 % yield as a yellow oil and as a mixture of diastereoisomers in a 1/1.5 ratio.




**287e** **321**

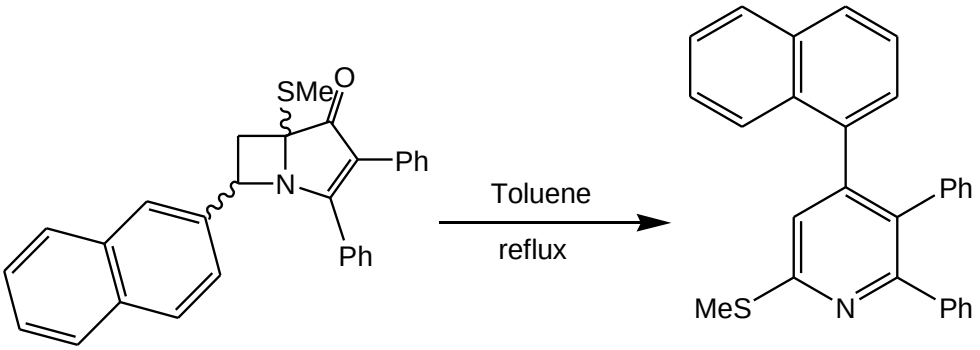
**Scheme 2.46**

The $^1H$ NMR spectrum showed a series of multiplets and three doublets of doublets between 7.98-6.72 ppm integrating as seventeen aromatic protons. All three protons of the four-membered ring appeared as two sets of signals showing the product as a mixture of diastereoisomers. Two sets of doublets of doublets at 5.74 and 4.48 ppm indicated the benzylic CH proton. One set of doublet of doublets appeared at 3.26 and 3.18 ppm for one proton of the $CH_2$, whereas another set of doublet of doublets appeared at 3.06 and 2.59. Two peaks at 2.13 and 2.07 evidenced the thiomethyl moiety and indicated the formation of the product as a diastereomeric mixture.

The structure of the product was further confirmed with $^{13}C$ NMR spectrum which showed double signals for carbons to confirm the presence of two diasteroisomers. Signals for the carbonyl appeared at 202.78 and 202.40 ppm whereas peaks for the alkene carbons of the enone appeared at 177.43, 175.45 and 126.00, 123.95 ppm. All other signals were consistent

with the assigned structure, including an extremely complex aromatic region that shows the expected number of CH and quaternary carbons for the diastereoisomeric mixture.

The naphthyl-substituted azabicyclic compound **321** was also heated in boiling toluene until disappearance of starting material had occurred. The pyridine **322** was isolated as white crystals in 64 % yield, after column chromatography.




**321** **322**

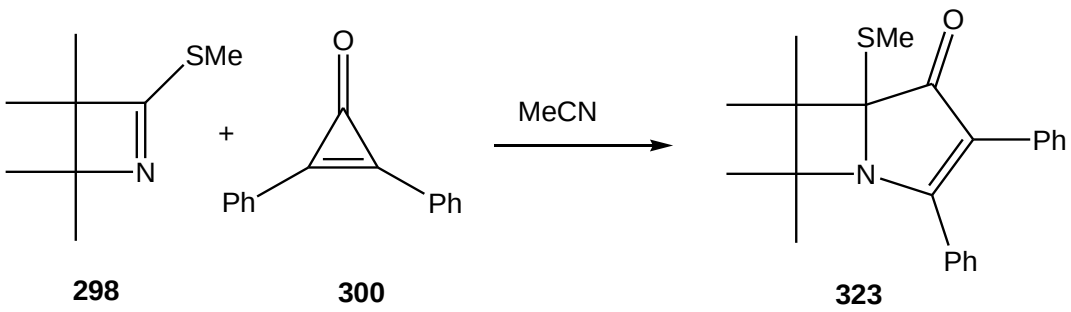
**Scheme 2.47**

Spectroscopic analysis provided the evidence for the structure of the product. IR spectrum showed there is no peak for the carbonyl which was present in the starting material. In the $^{1}H$ NMR spectrum a singlet at 2.7 ppm integrating to three protons showed the presence of the thiomethyl moiety. The rest of the signals were found in the aromatic region, most of them as multiplets confirming the eighteen protons of two phenyl, one naphthyl group and one proton of the pyridine ring. Pyridine ring formation was further evidenced by the $^{13}C$ NMR spectrum showing the loss of a carbonyl group from 202.78 and 202.40 ppm, also confirmed by IR spectroscopy, and loss of the carbon peaks of the four-membered ring. The presence of fourteen CH peaks and nine quaternary carbons in the aromatic region indicated that two phenyl groups and one naphthyl are substituted to the tetra-substituted pyridine ring whereas the fourth substituent SMe appeared at 13.42 ppm.

HRMS further confirmed the structure of the product as *2,3-diphenyl-4-naphthyl-6-methylthio-1-pyridine* with a mass of 404.1479 for a required mass of 404.1467.

### 2.3.2.3 Reactivity of 2-methylthio-3,3,4,4-tetramethyl-1-azetine with diphenylcyclopropenone : synthesis of 5-methylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo[3.2.0]hept-2-en-4-one.

After the successful reactivity of different 4-aryl-1-azetines with different cyclopropenones and subsequently converting the bicyclic adducts to pyridines, it was decided to investigate the reactivity of non-aryl azetines with cyclopropenones. Further exploration of the thermolyte reactivity of their products if they were found to produce bicyclic adducts similar to aryl azetines would then be carried out. Thus, 2-methylthio-3,3,4,4-tetramethyl-1-azetine **298**, which was synthesized from 2,3-dimethyl-but-2-ene, was reacted with diphenylcyclopropenone to afford *5-methylthio-2,3diphenyl-6,6,7,7-tetramethyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **323** in 51 % yield as a yellow solid.




**298** **300** **323**

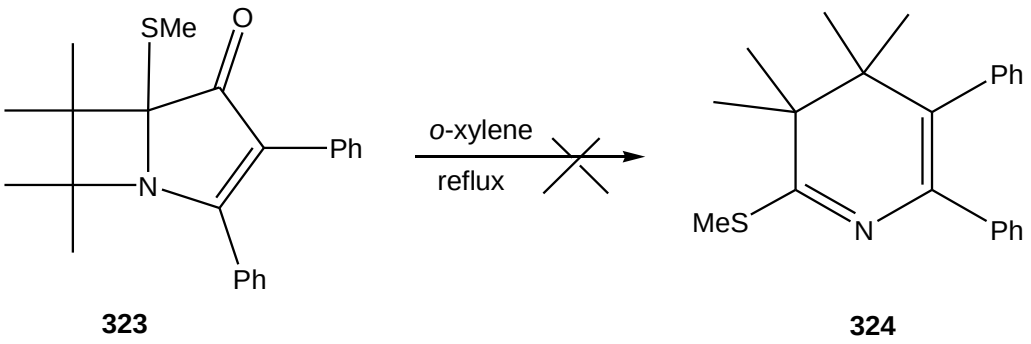
**Scheme 2.48**

To confirm the structure of the product, spectroscopic analysis of the compound was performed. Five singlets between 0.73-1.95 ppm in the $^{1}$H NMR spectrum, all integrating to three protons each, inferred the presence of the one thiomethyl and four methyl groups. Ten aromatic protons showed the presence of two phenyl groups.

The $^{13}$C NMR spectrum showed signals for five methyl groups between 10.60-27.96 ppm. The carbonyl peak appeared at 202.31 ppm whereas peaks for the unsaturated alkene carbons of the enone appeared at 175.63 and 123.57 ppm, respectively. The quaternary carbons of the four membered ring were evidenced by peaks at 41.93 and 70.30 ppm with the sp$^{3}$ bridgehead carbon at 83.79 ppm confirming the product as a bicyclic adduct. IR and HRMS further confirmed the structure of the product.

### 2.3.2.4 Reactivity of *5-methylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo[3.2.0]hept-2-en-4-one*.

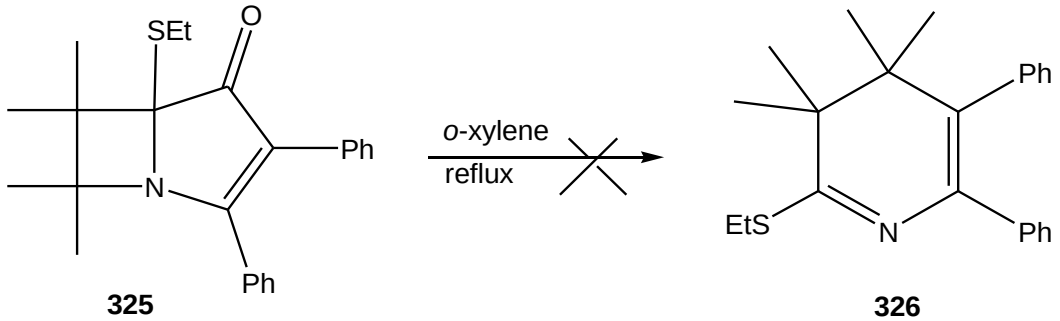
Based upon the successful thermolysis of other azabicyclic adducts to produce pyridines, this azabicyclic compound was also heated at elevated temperatures for 24 hours. However, no product was formed using a variety of solvents: indeed the compound was stable even after heating for 72 hours at 150 $^{o}$C in xylene.




**323** **324**

**Scheme 2.49**

The corresponding 5-ethylthio adduct **325,** formed from diphenylcyclopropenone and 2-ethylthio-3,3,4,4-tetramethyl-1-azetine, was found to be similarly stable and was also recovered unchanged after 72 h in xylene at reflux, as shown in Scheme 2.50.

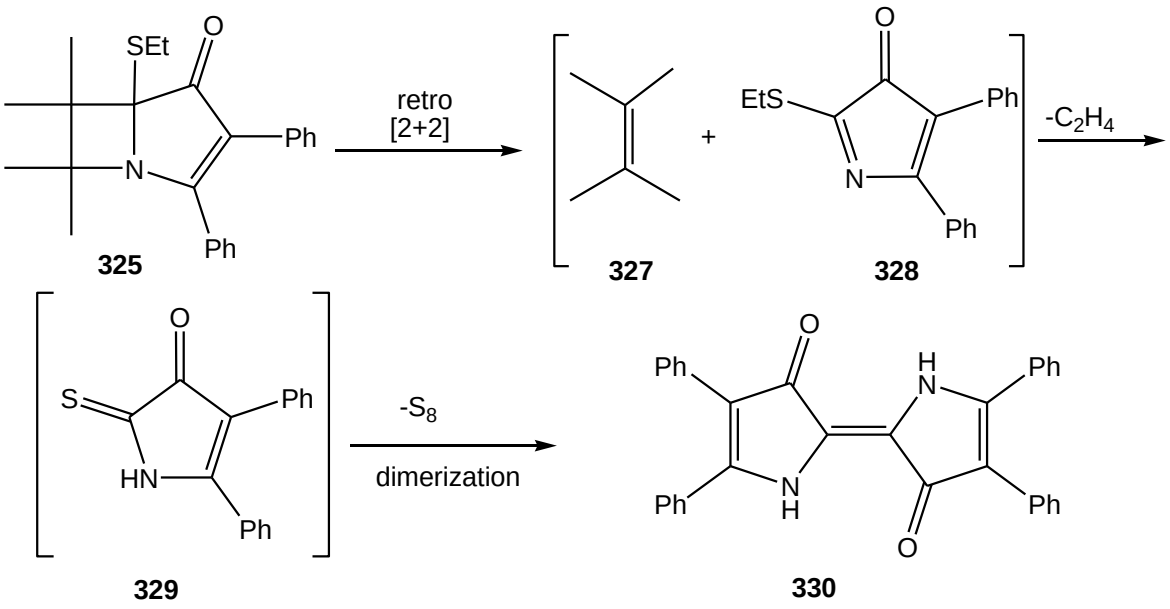



**325** **326**

**Scheme 2.50**

Interestingly, another worker in the group found in previous work that azabicyclic compounds produced from aliphatic substituted azetines behaved quite differently[229] with 5-ethylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo[3.2.0]hept-2-en-4-one **325** producing a bipyrrolinone through loss of alkene followed by dimerization with the loss of sulfur when

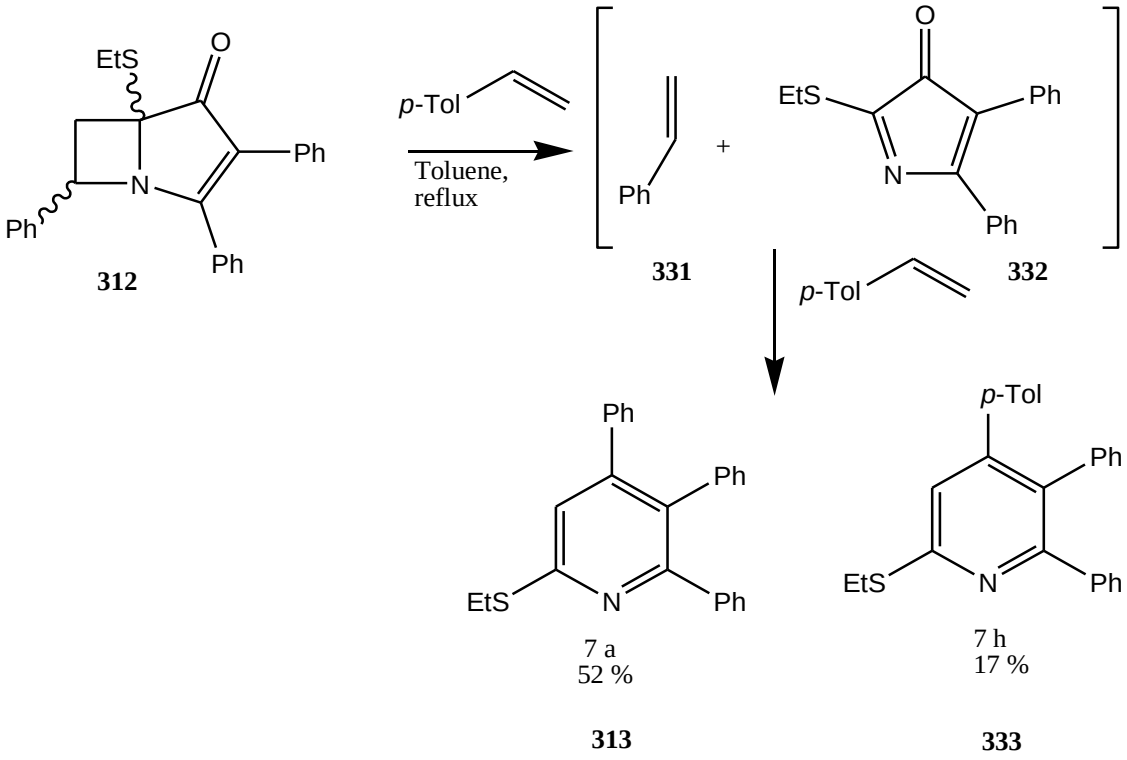
heated at ~180 $^{o}$C in boiling dichlorobenzene, a product whose formation (see Scheme 2.51) is consistent with the formation of intermediate **328**. Attempts to reproduce this reaction in this work were unsuccessful.




**Scheme 2.51**

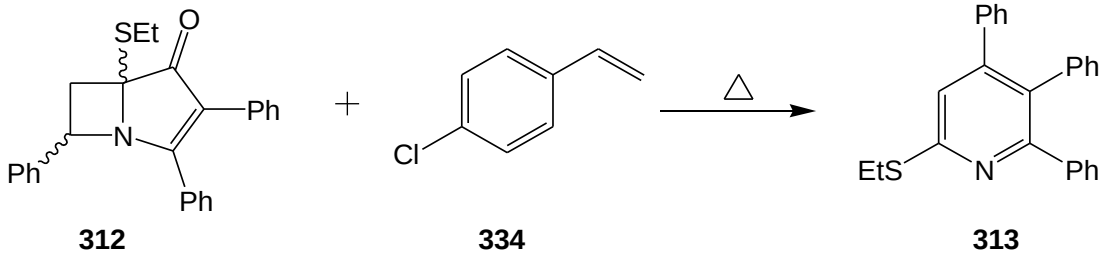
## 2.3.2.5 Attempts to trap the proposed intermediate azacyclopentadienone

To find evidence for our proposed mechanism for the synthesis of pyridines from azabicyclo[3.2.0]hept-2-en-4-ones via the formation synthesis of an azacyclopentadienone, some experiments were done in order to attempt to trap the intermediate azacyclopentadienone **332**.




**Scheme 2.52**

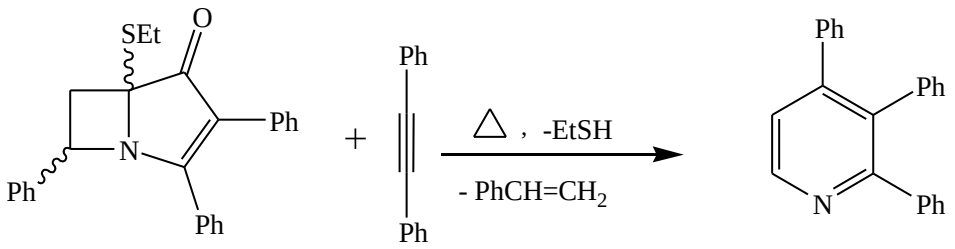
Earlier work done in the group (see Scheme 2.52, above) showed successful trapping of the azacyclopentadienone by introducing *p*-tolyl styrene into the reaction mixture to get two different pyridines as shown in the figure above. This reaction was successfully repeated but attempts to use other styrenes, such as the *p*-chlorostyrene **334** (shown below), were unsuccessful, with only a single pyridine being formed and no incorporation of the *p*-chloro substituent.




**Scheme 2.53**

In the next attempt to trap the azacyclopentadienone **332**, *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* **312** was reacted with diphenylacetylene **335** in boiling

toluene to afford the pyridine **336** with three phenyl groups and no thioethyl group as substituents, in 50 % yield.

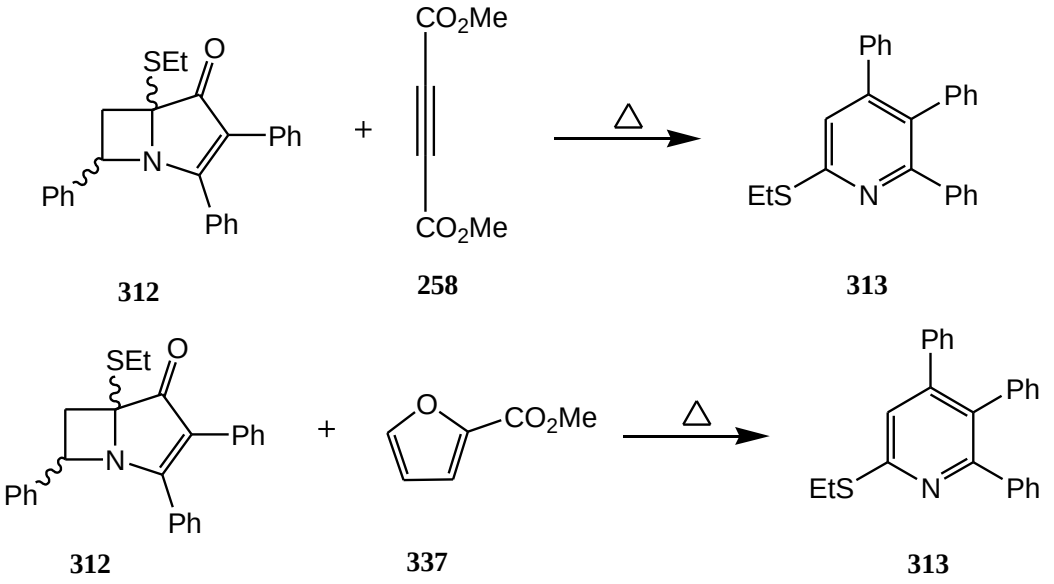



**312** **335** **336**

**Scheme 2.54**

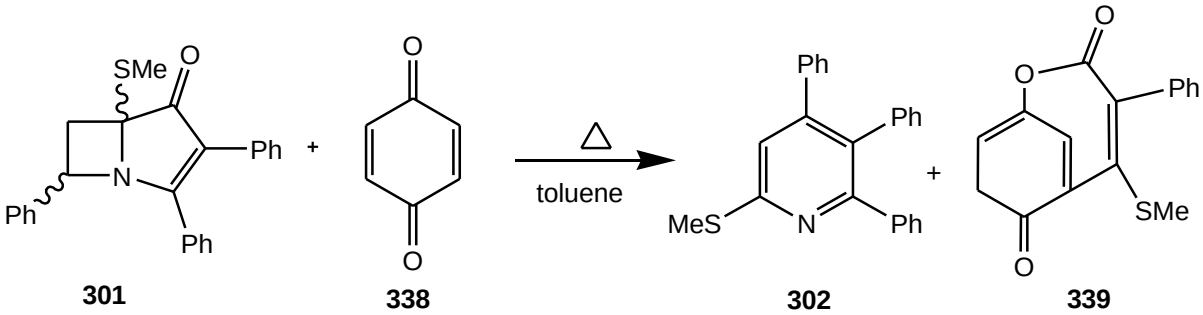
Alkynes are known to react with thiols to make alkenyl sulfides[230], and it is possible that the alkyne has promoted desulfurisation (as opposed to loss of hydrogen) of the expected dihydropyridine intermediate rather than reacted with the proposed azacyclopentadienone.
The spectroscopic analysis provided evidence for the structure of the product **336**. The $^{1}H$ NMR spectrum showed only signals in the aromatic region, with no signals for the ethyl moiety. Two doublets at 8.75 and 7.36 ppm with coupling constants of 7.3 Hz each confirmed the two protons of the pyridine ring. Fifteen other aromatic protons between 7.30-6.90 confirmed the presence of three phenyl groups. The $^{13}C$ NMR spectrum further confirmed the structure with the three phenyl substituents and tri-substituted pyridine showing seventeen signals between 158.38-123.69 ppm, with eleven CH signals and six quaternary carbons.

*5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* was also heated with DMAD **258**, because of its ability to act as dienophile in [4+2] cycloaddition reactions[231], and also with methylfuroate **337** (this time to act as a diene and trap the azacyclopentadienone as a dienophile)[232-235] in two different attempts to trap the intermediate azacyclopentadienone but in both cases the only product formed was the expected pyridine and in all cases no other product could be identified (Scheme 2.55).




**Scheme 2.55**

Based on the reactivity of *p*-benzoquinone **338** as a dienophile, it was investigated whether or not it may react with the proposed azacyclopentadienone. The reaction of 1,4-benzoquinone with *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* afforded two products: one was the expected pyridine **302** of adduct **301** in 65% yield, whereas the second product is an unknown, tentatively assigned compound **339**, as shown in Scheme 2.56, below.

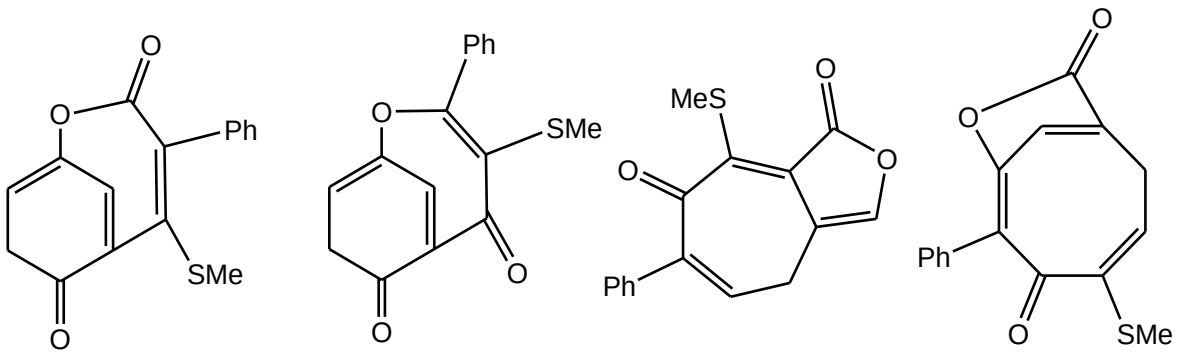



**Scheme 2.56**

Assuming the tentatively assigned structure is **339**, a singlet at 7.28 ppm in the $^{1}$H NMR spectrum corresponds to the isolated CH alkene and the C=CH-$CH_2$ moiety might explain a doublet (2H) at 3.77 ppm and a doublet of doublets at 6.12 ppm, signals that are clearly coupled. Five aromatic protons appear at 7.23-6.74 ppm and a singlet at 2.23 ppm appears for SMe. In the $^{13}$C NMR spectrum, two carbonyls appear at 187.7 and 187.4 ppm. Five other

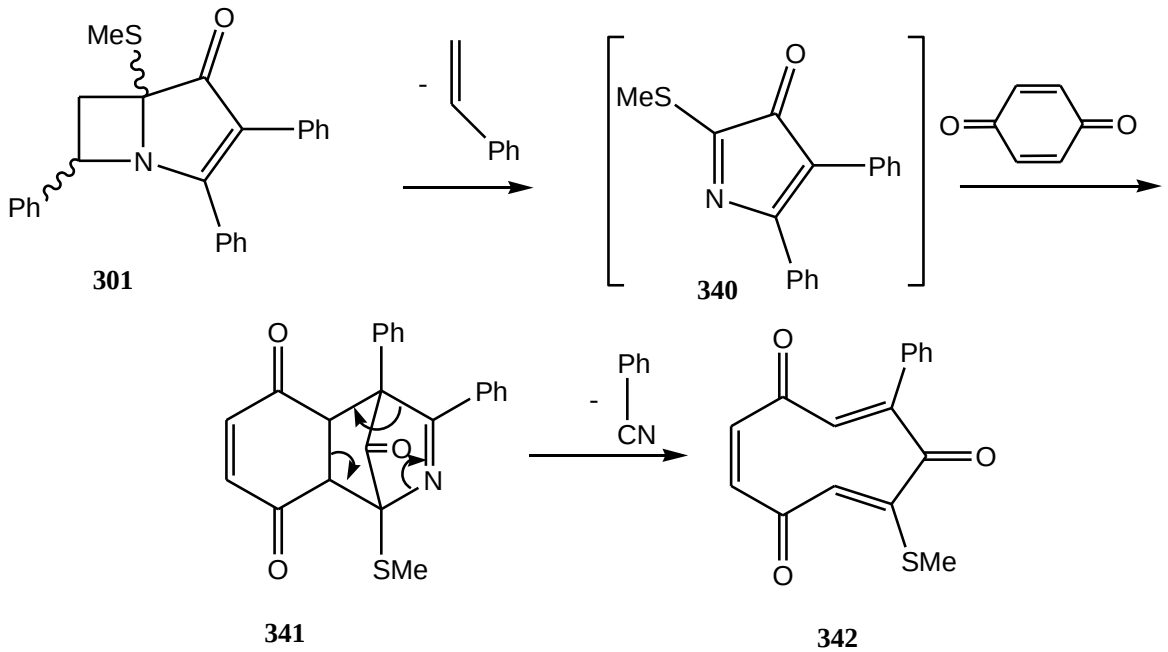
quaternary carbons and five CH peaks appear between 126 and 148 ppm. The $CH_2$ is at 32.64 and $CH_3$ at 19.40 ppm. IR and HRMS are also consistent with this tentative assignment.

It is possible to suggest several other structures **339b-339d** that fit the spectroscopic data.



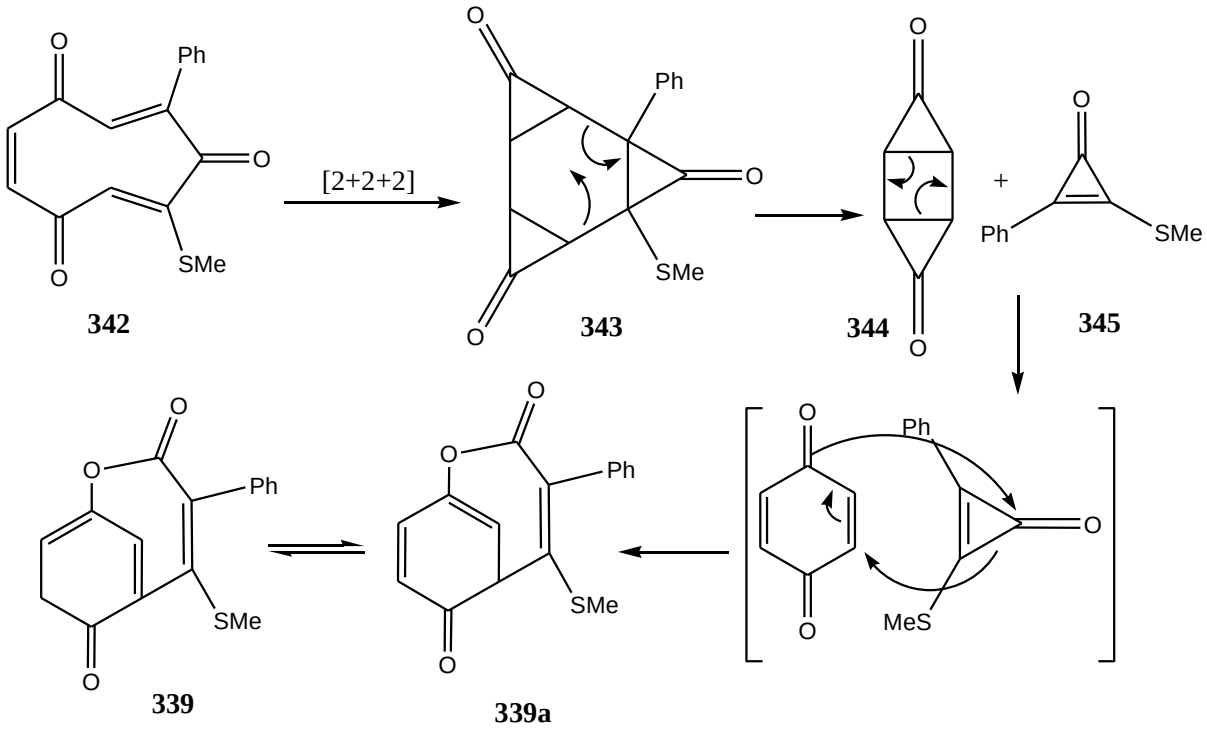

**Scheme 2.57**

However, only **339a** has a sensible mechanism, which, although again tentative is suggested below.




**Scheme 2.58**

This is the most obvious way for Ph, C and N to be lost. It is then suggested that intermediate **342** rearranges as follows, a process for which literature precedent exists [236-238].




**Scheme 2.59**

This interesting observation requires more work-unfortunately all attempts to crystallise the product for crystallographic analysis have been unsuccessful.

## 2.3.3 Reactivity of 1-azetines with 1,3-dipoles

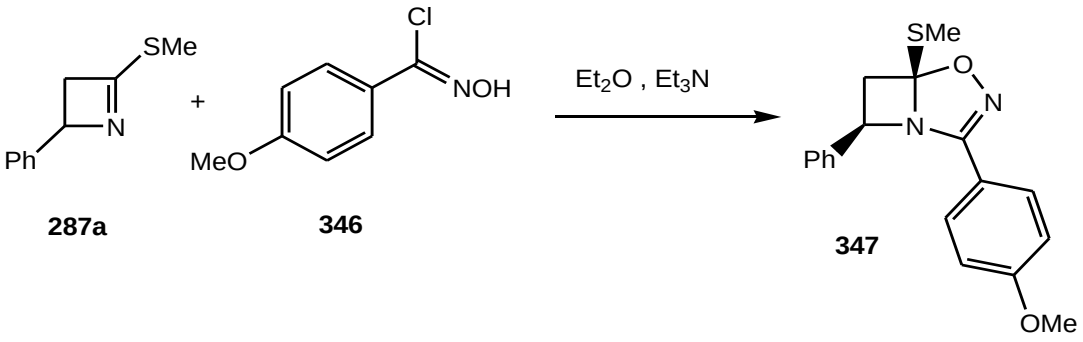
After successfully showing that 1-azetines undergo reaction with cyclopropenones to form bicyclic adducts and that these bicyclic adducts can also be subjected to further reaction to produce tetrasubstituted pyridines, it was envisaged that 1-azetines might undergo reaction with 1,3-dipoles like nitrile oxides to form bicyclic adducts which can undergo [2+2] cycloreversion on heating. It was anticipated that a heterocycle formed as a result of cycloreversion would, in the case of a nitrile oxide, be a 1,2,4-oxadiazole which would be isolable and not undergo the further reaction that was undergone by the proposed azacyclopentadienone, above.

## 2.3.3.1 Reactivity of 1-azetines with nitrile oxides.

Nitrile oxides were produced *in situ* from corresponding hydroximoylchlorides after dehydrochlorination[239-241] with triethylamine. Hydroximoylchlorides were formed as a result of chlorination[239] of aldoximes which in turn were produced from the corresponding aldehydes.

### 2.3.3.1.1 Reactivity of 2-methylthio-4-phenyl-1-azetine with *p*-methoxybenzohydroximoyl chloride : Synthesis of *2-(p-methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene*.

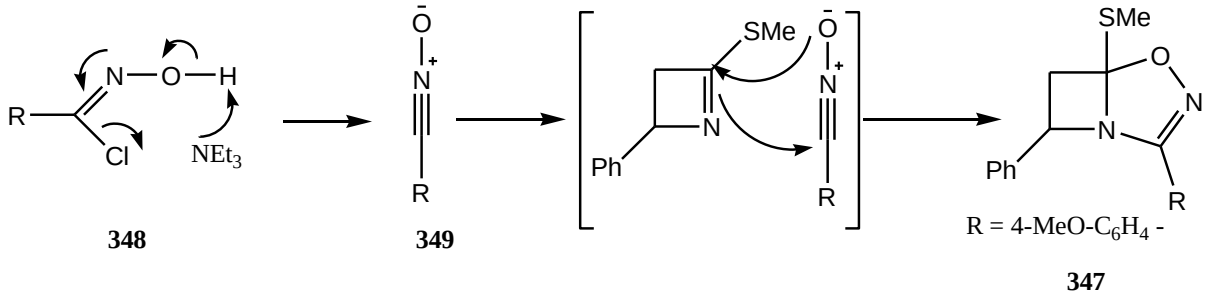
2-Methylthio-4-phenyl-1-azetine **287a** was reacted with *p*-methoxybenzohydroximoyl chloride **346** to afford 2-(*p*-methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diazabicyclo-[3.2.0]-hept-2-ene **347** in 43 % as yellow oil. *p*-Methoxy-phenyl nitrile oxide was generated *in situ* from *p*-methoxy-benzohydroximoyl chloride, with drop-wise addition of triethylamine to the reaction mixture. Triethylamine was added to produce nitrile oxide slowly to improve its reactivity with 1-azetine and to avoid nitrile oxide dimerisation which results in the formation of furoxans with only low yields of the desired oxadiazabicyclic adducts.




**287a** **346** **347**

**Scheme 2.60**

The mechanism involved for the synthesis of nitrile oxide and its reaction with 1-azetine is shown in Scheme 2.61 below.




**348** **349** **347**

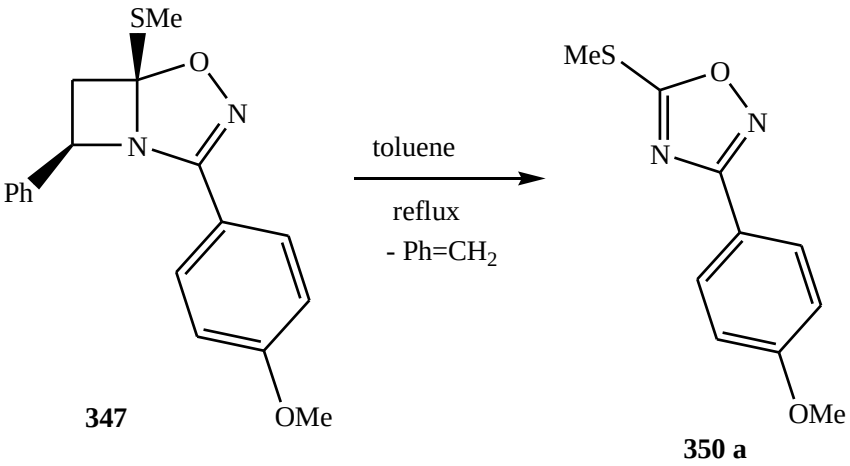
**Scheme 2.61**

The structure of the product **347** was deduced with the help of spectroscopic techniques. The $^{1}$H NMR spectrum indicated the presence of two aromatic rings by showing nine aromatic protons. The three protons of the four membered ring appeared as three doublets of doublets. The proton of the benzylic CH appeared as a doublet of doublets at 4.83 ppm with coupling constant 5.3 and 9.3 Hz indicating its coupling with both protons of $CH_2$ of the ring. Two more doublets of doublets at 3.67 and 2.72 ppm with $J$ = 9.3, 13.2, 13.2 and 5.3 respectively confirmed the coupling of two other protons of the ring with the benzylic CH proton. Two singlets at 3.8 and 2.2 ppm both integrating three protons each confirmed the presence of methoxy and thiomethyl moieties. The product was a single stereoisomer.

The $^{13}$C NMR spectrum further confirmed the structure by showing carbon of N=C-N at 161.7 ppm, three quaternary and five CH carbons in the aromatic region and the bridgehead quaternary carbon at 114.4 ppm confirming the bicyclic structure with two aromatic groups. Signals for the other four membered ring carbons appeared at 66.5 ppm and 44.6 ppm, whereas two peaks at 55.3 and 10.3 ppm confirmed methoxy and thiomethyl groups. IR and HRMS were also consistent with the assigned structure. It is notable that the product was a single diastereoisomer. There was no doubling up of peaks as was seen with the cyclopropenone adducts. NOESY experiments inferred the structure to have the *cis* stereochemistry between the phenyl and SMe groups, possibly as a result of the incoming 1,3-dipole approaching the 1-azetine *trans* to the existing phenyl group, thus forcing the SMe group *cis* to the phenyl substituent.

### 2.3.3.1.2 Reactivity of 2-(*p*-methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene : Synthesis of *3-(p-methoxy-phenyl)-5-(methylthio)-1,2,4-oxadiazole.*

As discussed above, thermolysis of the bicyclic adducts from 1-azetines and cyclopropenones produced interesting results. Thus adduct **347** was also heated in refluxing toluene to investigate if further interesting reactions could be discovered. The reaction was monitored by TLC which showed the disappearance of the starting material to afford the stable and isolable 1,2,4-oxadiazole **350a** as the only product in 88 % yield, produced via a formal overall [2+2] cycloreversion of the bicyclic adduct.



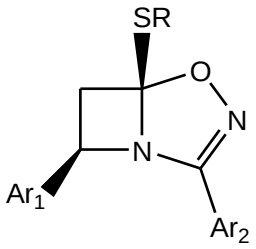

**347** **350 a**

**Scheme 2.62**

Spectroscopic analysis was performed to confirm the structure of the product. The $^{1}H$ NMR spectrum confirmed the presence of the *p*-substituted aromatic ring by showing two doublets at 7.99 and 6.98 ppm with a coupling constant of 8.0 Hz, integrating as two protons each. It also confirmed the loss of the four membered ring and of one phenyl group. Two singlet peaks at 3.85 and 2.78 confirmed the presence of $OCH_3$ and SMe, respectively. The $^{13}C$ NMR spectrum further confirmed the structure of the product by showing the C=N peak at 168.33 and $sp^2$ carbon connected to SMe at 178.05, whereas the SMe and OMe peaks appeared at 14.20 and 55.38 respectively. Two quaternary carbons and two CH peaks in the aromatic region completed the assignment of the structure of the product.

HRMS data confirmed the structure of the product by showing the mass (*m/z*) of 245.0350 required for 245.0355.

1,2,4-Oxadiazoles are most commonly constructed using 1,3-dipolar cycloadditions between nitrile oxides and nitriles[242,243] or from the reactions of a nitrile-derived amidoxime with a carboxylic acid derivative[244,245] as described in the introduction part of this thesis. In our methodology, the 1-azetine can be seen to be acting as an equivalent for the nitrile species RS–CN, known as either an alkyl thiocyanate or an alkyl thiocyanic ester. Based upon this result, it was decided to explore this reaction fully. This needed the synthesis of some other oxadiazabicyclo[3.2.0]hept-2-enes to act as precursors for 1,2,4-oxadiazoles. For this, a series of 1-azetines were reacted smoothly with nitrile oxides generated *in situ* from the corresponding benzohydroximoyl chlorides to give four other oxadiazabicyclo[3.2.0]hept-2-enes **351** as shown in the table below. These were also found to be single diastereoisomers having *cis* stereochemistry between SR and $Ar_1$ groups.




**351**

| No. | product | $Ar_1$ | R | $Ar_2$ | Bicycle % yield |
|---|---|---|---|---|---|
| 1 | **347** | phenyl | Me | 4-MeO-$C_6H_4$- | 43 |
| 2 | **351a** | 4-tolyl | Me | 4-MeO-$C_6H_4$- | 72 |
| 3 | **351b** | 4-tolyl | Et | 4-MeO-$C_6H_4$- | 48 |
| 4 | **351c** | 2-naphthyl | Me | 4-MeO-$C_6H_4$- | 44 |
| 5 | **351d** | 2-naphthyl | Me | 2-N3-$C_6H_4$- | 44 |

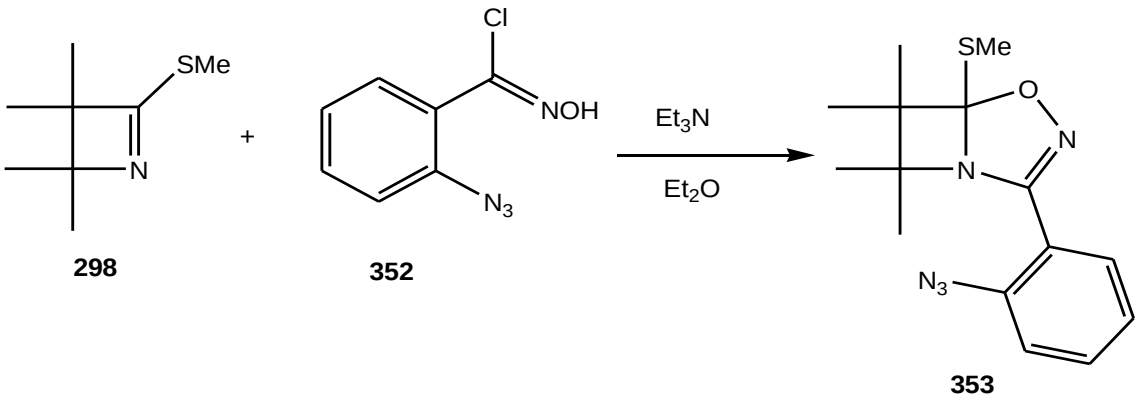
**Table 2.4.** Synthesis of oxadiazabicycles.

All of the required oxadiazabicycles were produced with the same methodology: 1,3-dipolar cycloaddition of the 1-azetines (see previous sections for synthesis) to a nitrile oxide that was generated from the corresponding hydroximoyl chloride by triethylamine induced dehydrochlorination. All adducts were formed as single diastereoisomers and all showed the same characteristics by NMR spectroscopy as described before: the $CH_2CH$ coupling in the ring, the characteristic bridgehead carbon that has the SR substituent.

The four new bicyclic systems 352a-d (see Table 2.4) were heated in toluene at reflux and produced the corresponding 1,2,4-oxadiazoles in yields of 82, 81, 87 and 68 %, respectively. The NMR spectra of the newly formed 1,2,4-oxadiazoles [351b-e: see experimental] were as expected and full details of these and the oxadiazabicycles are given in the experimental. HRMS and the IR spectra were also fully consistent.

#### 2.3.3.1.3 Reactivity of 2-methylthio-3,3,4,4-tetramethyl-1-azetine with 2-azidobenzohydroximoyl chloride : Synthesis of *2-(2-azidophenyl)-5-(methylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diaza-bicyclo-[3.2.0]-hept-2-ene.*

The successful reactivity of aryl azetines with nitrile oxides to produce interesting results lead us to think about using other azetines with aliphatic substituents, to investigate if they can also produce something interesting. 2-Methylthio-3,3,4,4-tetramethyl-1-azetine was therefore reacted with 2-azidobenzohydroximoyl chloride in the presence of triethylamine to yield the corresponding cycloadduct **353** in 52 % as a yellow oil. The azide was chosen due to the interesting chemistry of the azide group[246] and potential for further reactions.




**Scheme 2.63**

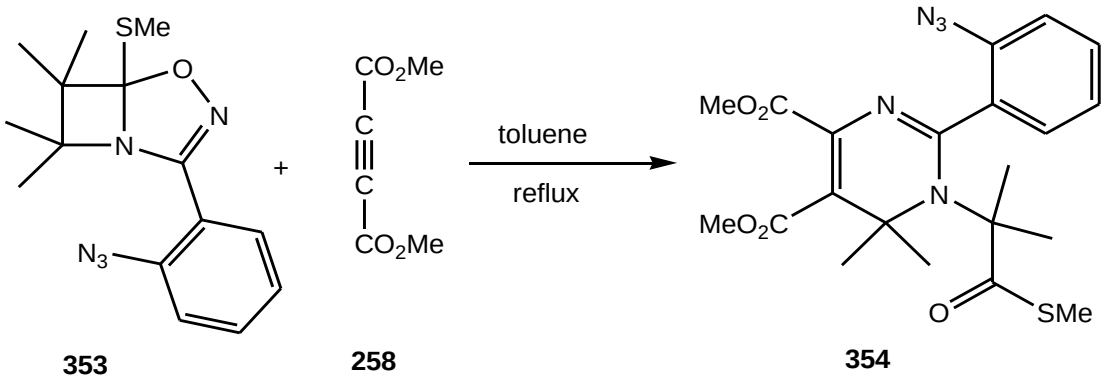
$^{1}$H NMR spectroscopy confirmed the four protons of aromatic ring with four signals at 7.14, 7.25, 7.43 and 7.66 ppm. The four methyl groups attached to the four membered ring appeared as singlets at 0.97, 1.26, 1.32 and 1.50 ppm whereas the thiomethyl group was confirmed as a singlet at 2.1 ppm.

$^{13}$C NMR spectroscopy further confirmed the structure of the product. Two quaternary and four CH aromatic carbon signals appeared at 138.36, 118.80, 131.54, 130.77, 124.68, 119.83 ppm. The $sp^2$ carbon (C=N) attached to the aromatic ring appeared at 157.36 ppm whereas the $sp^3$ quaternary bridgehead carbon appeared at 117.14 ppm. The two remaining quaternary carbons of the four membered ring appeared at 71.85 and 52.75 ppm, and the four methyl groups attached to the four membered ring and thiomethyl group were confirmed with $CH_3$ signals at 26.65, 21.09, 20.52, 20.13 and 9.69 ppm.

The IR spectrum confirmed the presence of the azide moiety, and the MS data showed the expected relative molecular mass assigned to the structure of the product.

#### 2.3.3.1.4 Reactivity of *2-(2-azidophenyl)-5-(methylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* with DMAD : Synthesis of *dimethyl 2-(2-azidophenyl)-6,6-dimethyl-1-(methyl-2´[methyl-3´-oxopropan-2´-yl]thiocarboxylate)-1,6-dihydropyrimidine-4,5-dicarboxylate.*

The thermolysis of bicyclic adducts made from 1-azetines produces interesting results as detailed above. Simple heating of compound **353** in toluene or xylene at reflux produced no results. It was therefore decided to investigate the reactivity of bicyclic compound **353** in the presence of DMAD. With the azide group present in the bicyclic adduct **353**, it was envisaged that DMAD being a good dipolarophile would add to the azide, allowing the synthesis of triazolo-oxadiazolo substituted benzenes. The reaction was performed in refluxing toluene overnight to afford a complex unexpected product as a yellow oil to which structure **354** was assigned in 36 % yield.



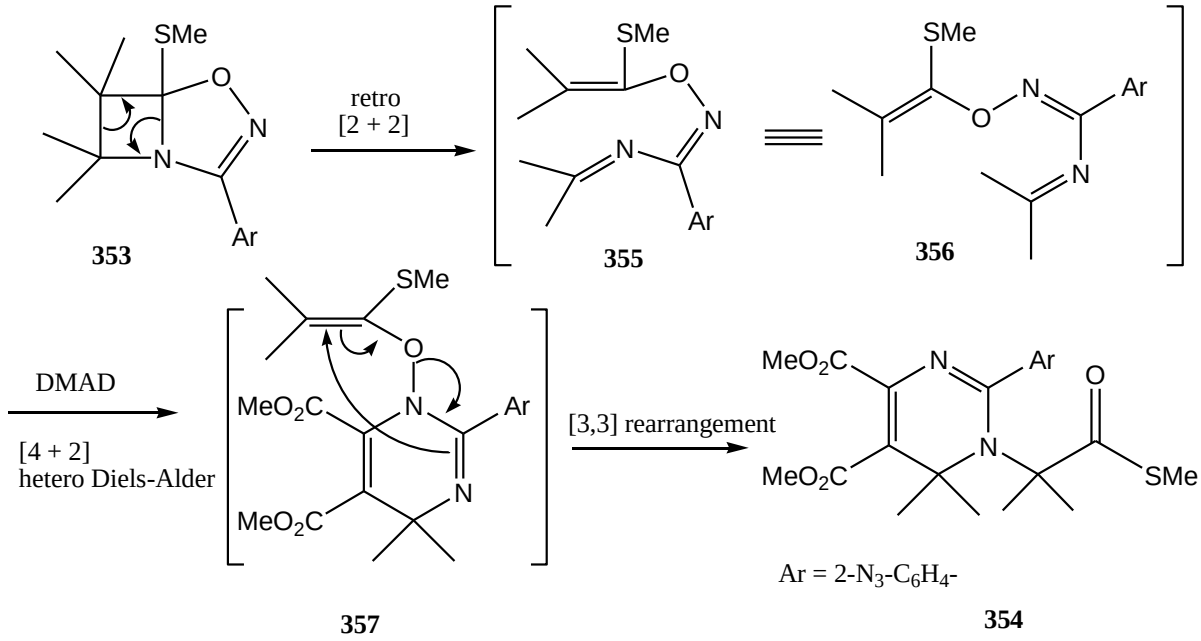

**353** **258** **354**

**Scheme 2.64**

The structure of the product was assigned by spectroscopic analysis. The $^{1}$H NMR spectrum showed four signals for four aromatic protons between 8.26-7.27 ppm indicating the presence of the aromatic ring. Two singlets at 4.01 and 3.74 both integrating to three protons indicated the presence of two methoxy groups, whereas a singlet at 2.25 confirmed the presence of the thiomethyl group. Two peaks at 1.46 and 1.31 integrating to six protons each indicated the the presence of four methyl groups.

The $^{13}$C NMR spectrum showed a signal at 204.66 ppm for the carbonyl connected to SMe, with two more carbonyl signals at 160.43 and 158.20 ppm for the carbonyls of the methyl esters. A quaternary carbon at 165.18 indicated the N-C=N carbon. $^{13}$C NMR spectoscopy confirmed the presence of six aromatic carbons, two sp$^3$ carbons connected to the dimethyls at 64.77 and 55.51 ppm respectively, and two methoxy signals at 53.30 and 52.71 ppm. The signal for the SMe appeared at 12.08 ppm and the final two quaternary carbons of the pyrimidine appeared at 133.07 and 131.96 ppm. The IR spectrum confirmed the presence of an azide group, confirming it had not reacted with DMAD, with absorption at 2129 cm$^{-1}$ and a strong carbonyl peak at 1732 cm$^{-1}$. Mass spectrometry further supported the structure with measured mass (*m/z*) of 482.1472 for required mass of 482.1468.

The suggested mechanism for this reaction proceeds via a [2+2] cycloreversion of the bicyclic adduct to produce a heterodiimine which then undergoes [4+2] hetero-Diels-Alder reaction with DMAD to form a six membered ring, and then a [3,3] sigmatropic rearrangement leading to the synthesis of the final product.




**Scheme 2.65**

This reaction has also found to be successful with the SEt analogue, producing a second example of the pyrimidine, this time as the ethyl thiocarboxylate[247].

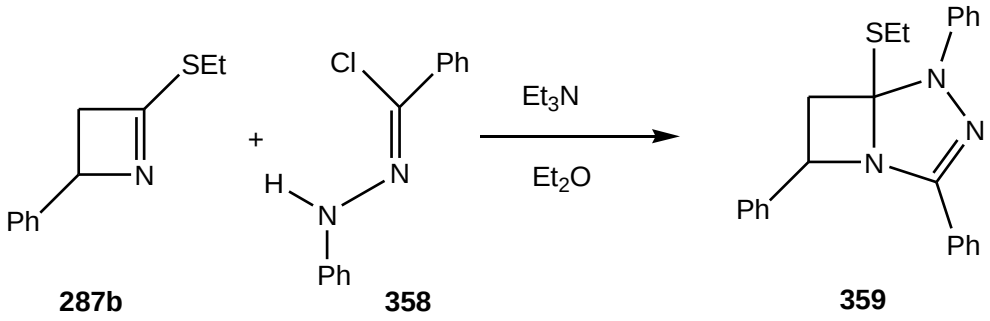
## 2.3.3.2 Reactivity of a 1-azetine with a nitrile imine

After successfully exploring the reactivity of 1-azetines with nitrile oxides, it was decided to investigate the reactivity of 1-azetines with nitrile imines and the further reactivity of their bicyclic adducts if an initial model study produced anything interesting.

The 1-azetine was synthesized by the method described above and the nitrile imine was generated *in situ* from α-chlorobenzaldehyde phenylhydrazine as a result of dehydrohalogenation with triethyl amine. α-Chlorobenzaldehyde phenylhydrazine was produced as a result of chlorination of β-benzoyl phenylhydrazine **358** which was in turn was made from phenylhydrazine.

**2.3.3.2.1 Reactivity of 2-ethylthio-4-phenyl-1-azetine with α-chlorobenzaldehyde phenylhydrazine : Synthesis of *2,4,7-phenyl-5-(ethylthio)-1,3,4-triazabicyclo[3.2.0]hept-2-ene.***

The reaction of 1-azetine **287b** with α-chlorobenzaldehyde phenylhydrazine in the presence of TEA afforded the bicyclic adduct **359** in 20 % as a yellow oily solid.




**287b** **358** **359**

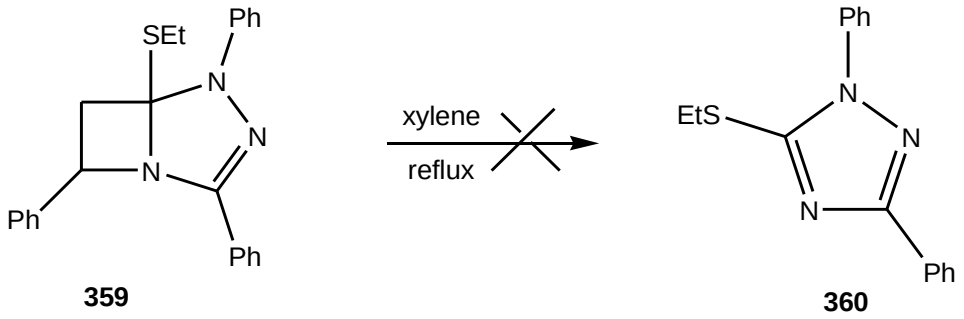
**Scheme 2.66**

The structure of compound **359** was confirmed by spectroscopic analysis. The $^{1}H$ NMR spectrum confirmed the presence of fifteen aromatic protons for the three phenyl groups. The proton of the four membered ring CH appeared as a doublet of doublets at 4.54 with coupling constant of 9.3 and 5.3 Hz. The two other protons of this ring appeared as a multiplet at 3.37 ppm. A doublet of quartets at 3.37 ppm indicated the presence of the two diastereotopic protons of the thioethyl methylene with a triplet at 1.15 ppm with coupling constant of 7.3 Hz for the methyl. The $^{13}C$ NMR spectrum confirmed the structure by showing three quaternary and nine CH carbon signals for the presence of the three phenyl groups. The signal for the C=N appeared at 161.58 ppm with the $CH_2$ and CH of the four membered ring appearing at 48.01 and 33.85 ppm. Two peaks at 25.54 and 14.39 ppm completed the spectrum and confirmed the presence of thioethyl group. MS data was fully consistent with the assigned structure.

The compound was a single diastereoisomer, but the relative stereochemistry was not determined.

Based on the previous results obtained from the thermolysis of bicyclic adducts made from 1-azetines, it was hoped that bicyclic adduct **359** would behave in the same way to produce a triazole and a styrene as a result of [2+2] cycloreversion of the compound. Unfortunately, no such reaction was observed under a variety of conditions, including up to 3 days in xylene at

reflux. The failure of this model system meant that other nitrilimine adducts were not explored.



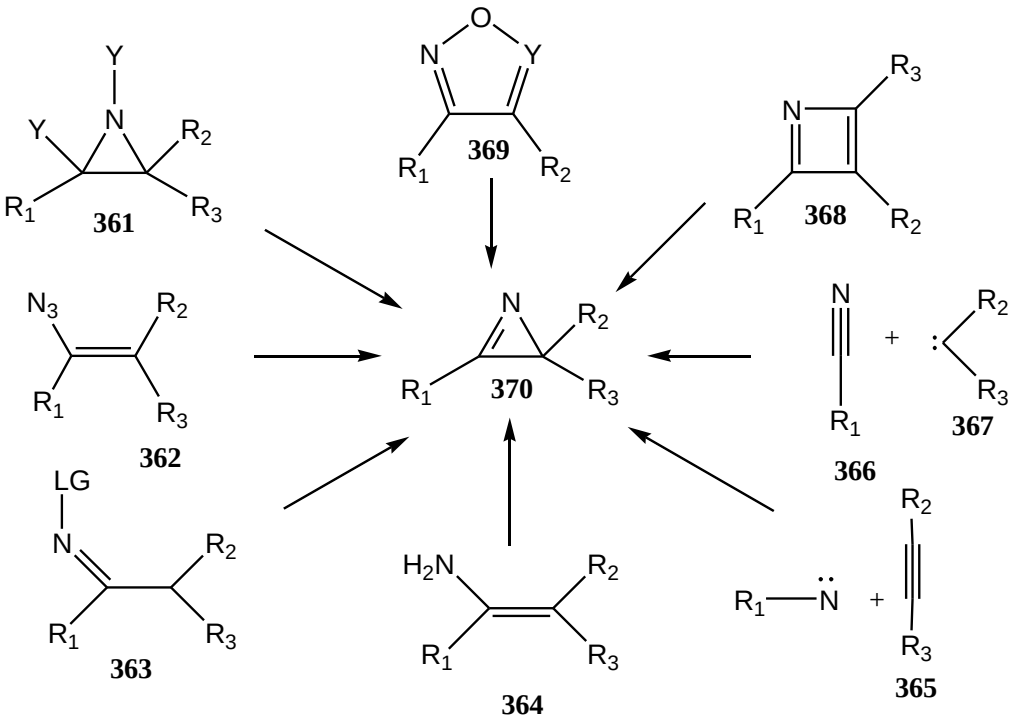

**359** **360**

**Scheme 2.67**

## 2.4 Synthesis and reactivity of 2H-azirines

The successful investigation of the chemistry of 1-azetines with cyclopropenones and 1,3-dipoles prompted us to turn our focus to 3-membered cyclic imines, 2H-azirines. 2H-Azirines have been extensively studied due to their potential in the synthesis of N-containing heterocycles and functionalized amino derivatives[248-250].

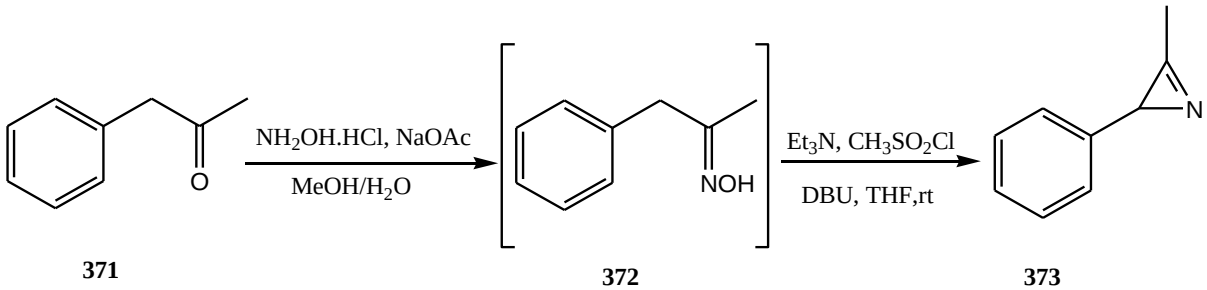
Among the synthetic strategies (Scheme 2.68) for the preparation of 2H-azirines[248-251], the most widely used route is the Neber process which is an intramolecular reaction of N-functionalized imines **363**[249,252]; other routes include pyrolysis or photolysis of vinyl azides **362**[249,253,254], and ring contractions of isoxazoles **369**[255,256], oxazophospholes[257,258] and azete derivatives[259] **368**. Elimination reaction[260,261] or Swern oxidation of aziridine derivatives[262,263] **361** can also produce 2H-azirines. 2H-Azirines can also be synthesized via intermolecular reactions between nitriles and carbenes[264-266] or nitrenes and acetylenes[267,268]. Synthesis of 2H-azirines has been performed by using various substituted enamine derivatives **364** in the presence of phenyliodine (III) diacetate (PIDA)[269] and in a recently reported strategy, free carbenes produced from α-diazo oxime ethers have been used to produce 2-alkyl/aryloxy 2H-azirines[270].




**Scheme 2.68**

## 2.4.1 Synthesis of 2-methyl-3-phenyl-1-azirine

For the purpose of this work, 2-methyl-3-phenyl-1-azirine was synthesized using the Neber reaction[271], starting with phenylacetone which was converted to the oxime by using hydroxylamine hydrochloride and sodium acetate. Methanesulfonyl chloride was used to make the ketoxime mesylate which was converted into the 2H-azirine with the help of DBU in 55 % yield and isolated as colourless oil.

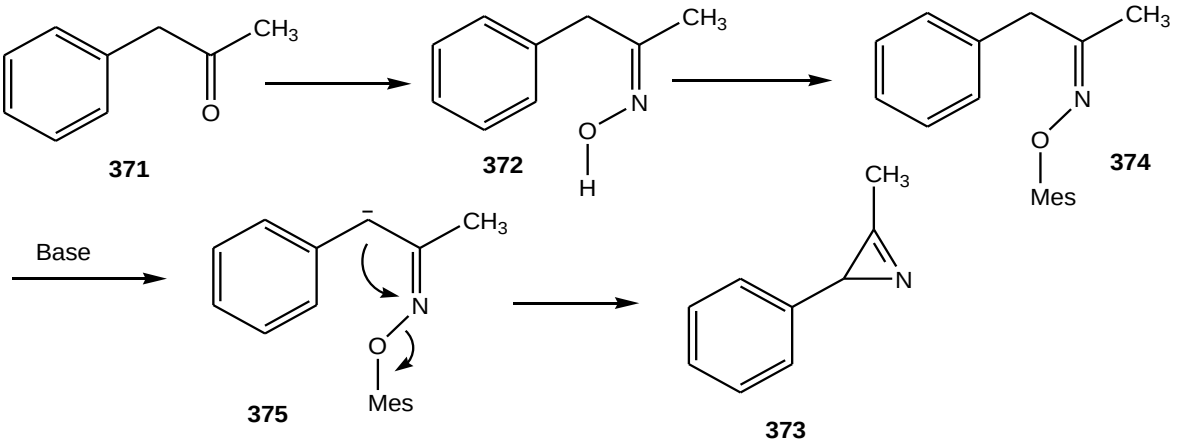



**371** **372** **373**

**Scheme 2.69**

Spectroscopic analysis and comparison to literature data [254] confirmed the structure of the product. The $^{1}H$ NMR spectrum showed a singlet integrating to three protons to confirm the presence of the methyl group and another singlet integrating to one proton which confirmed the CH of the ring. Five aromatic protons showed the presence of the aromatic ring. The $^{13}C$ NMR spectrum was consistent with the structure of the product showing the C=N signal at 164.44 ppm, one quaternary and three CH signals in the aromatic region. A peak at 12.85 ppm confirmed a methyl group and a signal at 33.39 ppm confirmed the CH of the ring.

The mechanism of the reaction involves synthesis of a ketoxime mesylate, which after basification (DBU) forms a carbanion which substitutes the mesylate group in a nucleophilic displacement reaction to form the azirine ring.

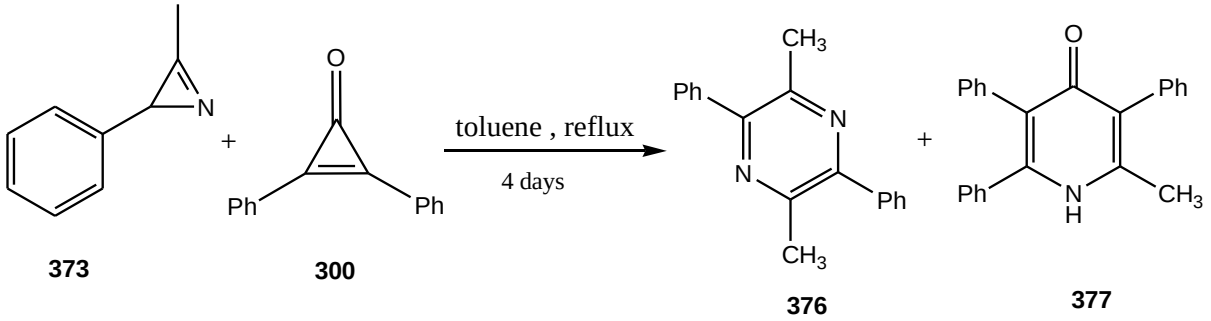



**Scheme 2.70**

## 2.4.2 Reactivity of 2-methyl-3-phenyl-1-azirine with diphenylcyclopropenone : Synthesis of 2,5-dimethyl-3,6-diphenylpyrazine and 2-methyl-3,5,6-triphenylpyridine-4-(1*H*)-one.

As the aim of this project was to investigate the reactivity of cyclic imines with cyclopropenones and 1,3-dipoles, the 1-azirine was mixed with diphenylcyclopropenone, a process reported to produce a pyridine derivative by Hassner[272] sometime ago, but unexplored since. 2-Methyl-3-phenyl-1-azirine was mixed with DPP in toluene at reflux to afford, in fact, two products. One was 2-methyl-3,5,6-triphenylpyridine-4-(1H)-one **377** (Scheme 2.71)

isolated in 5 % yield as a yellow solid and the second was characterized as 2,5-dimethyl-3,6-diphenylpyrazine **376** in 19 % yield as a yellow solid. The minor product was that expected from the work of Hassner, although in much lower yield, and the major product was unexpected but, as described below, predictable.



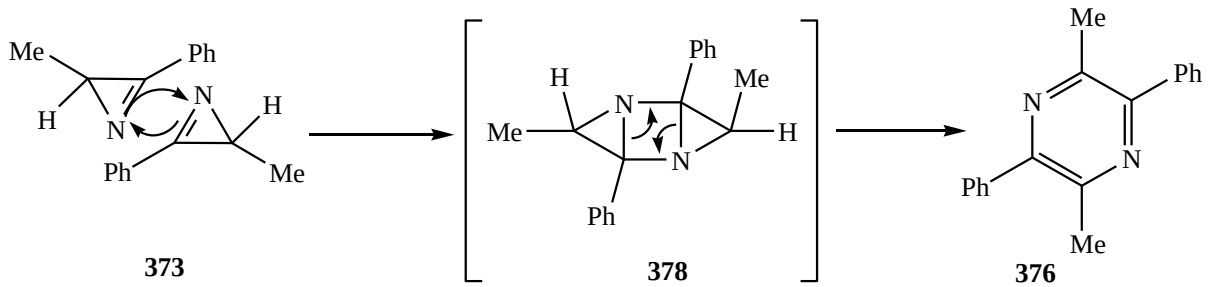

**373** **300** **376** **377**

**Scheme 2.71**

**Spectroscopic analysis of 2,5-dimethyl-3,6-diphenylpyrazine.**

The $^{1}H$ NMR spectrum showed a singlet at 2.64 ppm integrating to six protons which confirmed the presence of two methyl groups. A multiplet centred on 7.42 ppm showed the presence of six aromatic protons and this together with a doublet at 7.63 ppm integrating for four protons, showed the presence of the two phenyl groups. In the $^{13}C$ NMR spectrum a signal at 22.69 ppm confirmed two methyl groups whereas four signals in aromatic region confirmed two phenyl groups. One signal at 151.08 ppm appeared for C=N with another quaternary carbon at 147.84 ppm which confirmed the formation of pyrazine. Mass spectrometric data further confirmed the structure of the product.

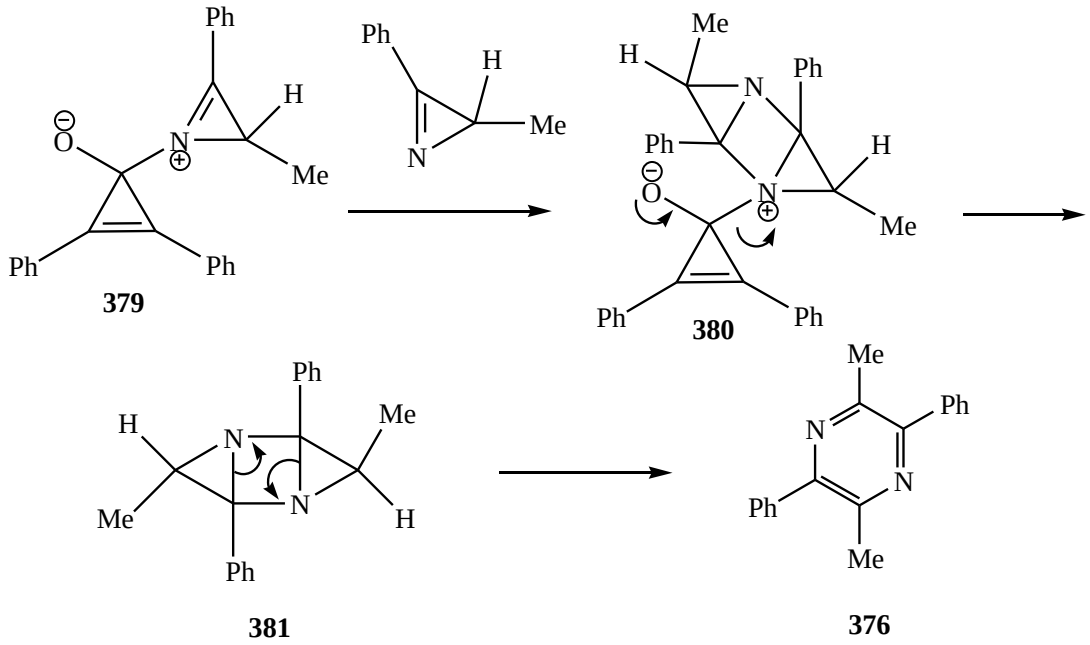
The mechanism of the reaction most likely involves the dimerization of the azirine ring to form a four membered ring **378** followed by the ring opening to form the pyrazine ring.




**373** **378** **376**

**Scheme 2.72**

When this reaction was repeated without DPP, no product was formed even after five days of refluxing the azirine in toluene. It would therefore appear that DPP acts as a catalyst for the synthesis of the pyrazine. The use of DPP as a catalyst for some reactions has gained recent interest[273,274] in the literature. On the basis of these reports, it is possible that the cyclopropenone activates the azirine to dimerisation as shown below.

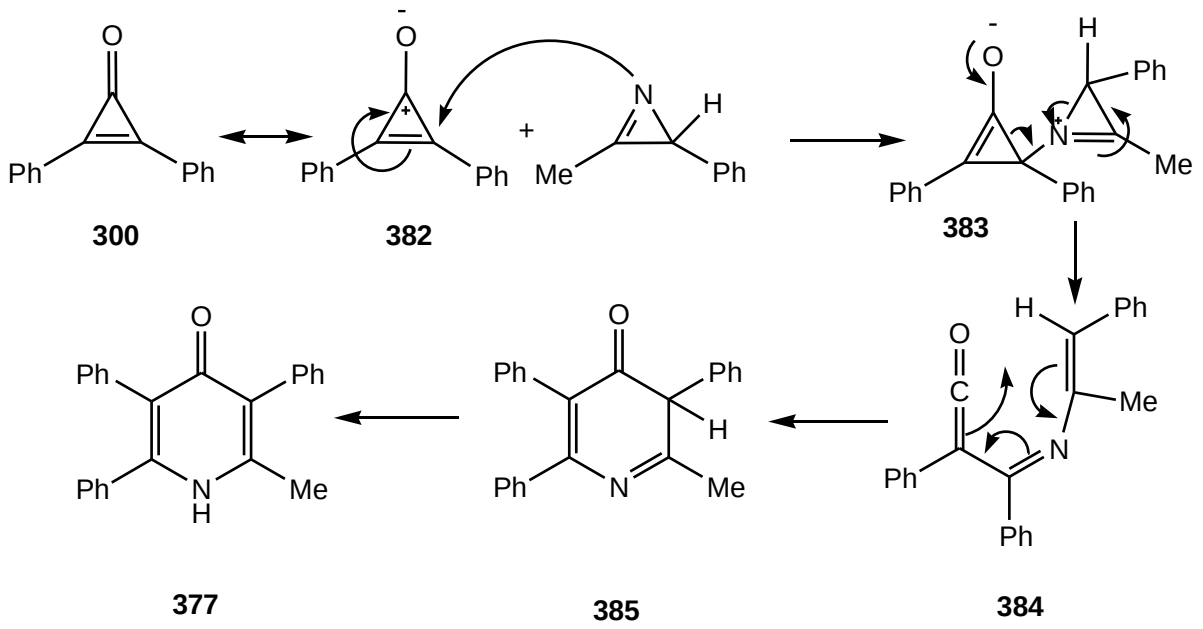



**Scheme 2.73**

**Spectroscopic analysis of 2-methyl-3,5,6-triphenylpyridine-4-(1*H*)-one.**

The $^{1}$H NMR spectrum and the work of Hassner allowed us to assign the structure to the product **377** in Scheme 2.71. A singlet at 2.63 ppm integrating to three protons and a broad singlet at 7.95 confirmed the presence of methyl and amine groups respectively. The rest of signals appeared in the aromatic region showing the presence of fifteen protons to confirm three phenyl groups. In the $^{13}$C NMR spectrum a quaternary carbon at 172.64 ppm indicated the presence of carbonyl moiety and a signal at 25.66 presented evidence for the methyl group. The presence of seven additional quaternary carbons and nine CH signals in the region 123.91-166.97 ppm confirmed the presence of three phenyl groups and formation of pyridone ring. The product was identical to that isolated by Hassner[272].

The proposed mechanism of the reaction involves nucleophilic attack of the azirine nitrogen on the electrophilic cyclopropenone ring followed by an intramolecular Cope cyclization to form the pyridine-4-one ring[272].

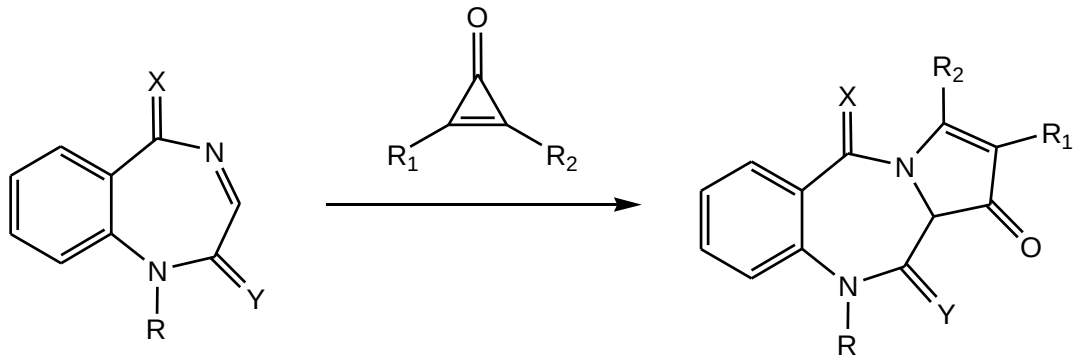



**Scheme 2.74**

Further examples of this process are being sought in the group, but time limits prevented further exploration in this work.

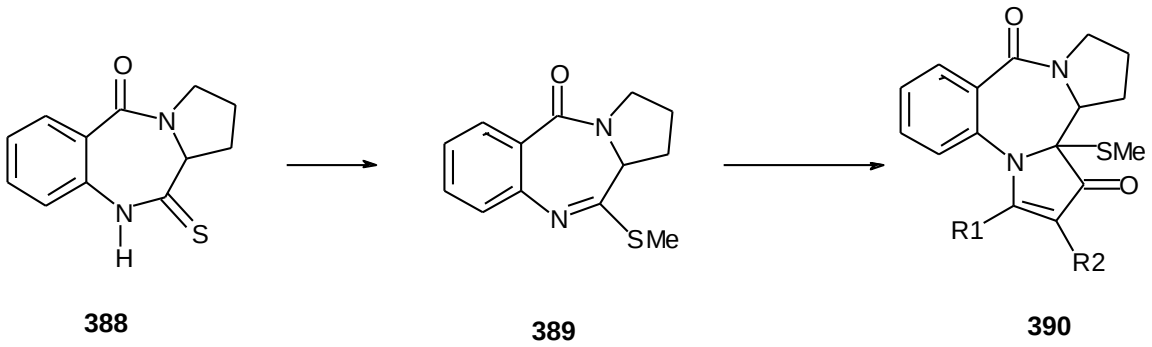
## 2.5 Synthesis and reactivity of benzodiazepines

The aim of this part of the PhD project was to explore the reactivity of the imine function of a series of relevant benzothiadiazepines and benzodiazepines towards cyclopropenones and nitrile oxides. So, the first target was to develop a method for the synthesis of the required benzodiazepines and then convert them to imines using either the thionation and S-alkylation process already discussed or direct O-alkylation. It was anticipated as part of this strategy that cyclic imines made from benzodiazepines in this way would react with cyclopropenones to form highly sought pyrrolobenzodiazepines[275-277] as shown below. However, a wide range of other benzodiazepines and benzothiadiazepines based imines was also targeted.




**Scheme 2.75**

In another goal it was hoped to use a series of pyrrolobenzodiazepines themselves as starting materials for the synthesis of tetracyclic pyrrolobenzodiazepines:




**Scheme 2.76**

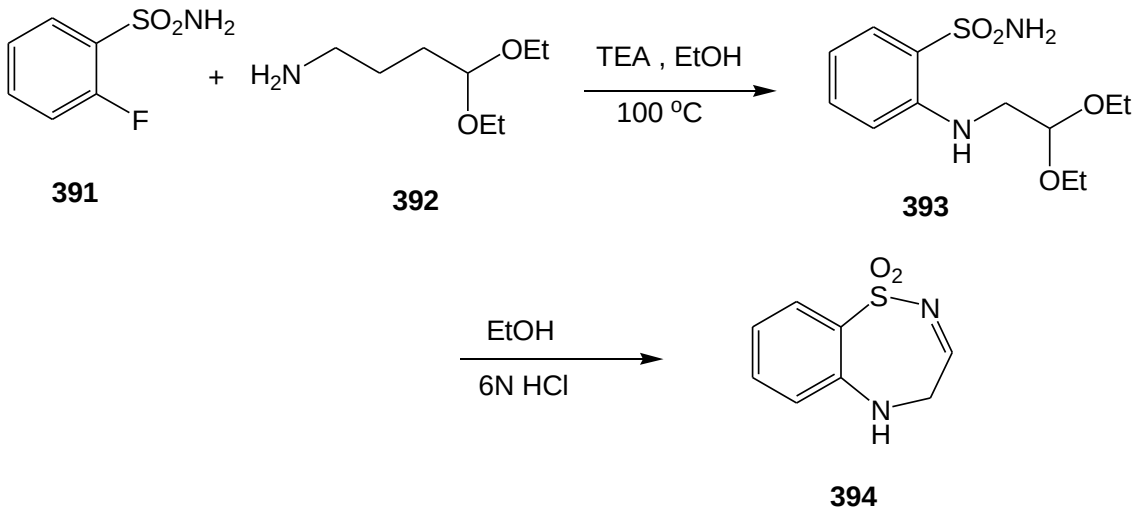
In the same way such imines can be used to form oxadiazolobenzodiazepines and oxadiazolopyrrolobenzodiazepines by reacting with nitrile oxides, rather than cyclopropenones.

## 2.5.1 Synthesis of benzodiazepines

Benzodiazepines have attained much attention in recent years as an important class of heterocycles due to their important biological and pharmaceutical activities, such as anti-inflammatory, antianxiety, sedative, anticonvulsant, hypnotic and antidepressive activities. The pyrrolobenzodiazepines (PBDs) are a class of antitumor antibiotics which act as DNA interacting agents[275]. There are many methods available for the synthesis of PBDs[275].

Intramolecular aza-Wittig reaction has been used to synthesize the natural DC-81 antibiotic starting from *o*-azidobenzoyl chloride and L-prolinol. As a result of this, the imine bond was formed directly and the cyclization occurred under mild reaction conditions[276]. PBDs have also been synthesized from 2-nitrobenzoic acid and (2S)-proline followed by amide formation and use of tetra-n-propylammonium peruthenate (TPAP) for conversion of secondary amine to its imine form[277].

As a first step to synthesize a wide range of benzodiazepines with a useful imine function for PBD analogue synthesis an attempt was made to synthesize a 1,2,5-benzothiadiazepine by using a method described by Whitehead and Traverso[278]. 2-Sulfamoylfluorobenzene was reacted with aminoacetaldehyde diethylacetal to afford 2-sulfamoyl-N-β,β-diethoxyethylaniline in 42 % yield. After confirming the structure of the product, it was treated with 6N HCl in order to liberated the aldehyde and allow subsequent cyclization. Unfortunately, this latter reaction was unsuccessful and the desired benzothiadiazepine (**394**) could not be isolated.

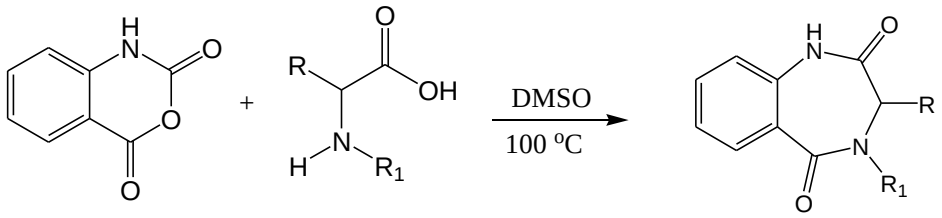



**391** **392** **393** **394**

**Scheme 2.77**

A straightforward one-step method developed by Wright and Brabander[279] was used to synthesize benzodiazepinones which can be turned into imines after thionation and alkylation. Thus isatoic anhydride was heated with different amino acids and amino acid esters and different benzodiazepines were formed as a result of a condensation reaction. By using pipecolic acid and thiazoline-4-carboxylic acid, tricyclic PBD analogues were formed, while using other amino acid esters some more benzodiazepines were formed with different

substitutents in good yield. All these compounds had their structures confirmed by NMR spectroscopy, and all have already been reported in the literature and synthesized using this exact method[280].




**395** **396** **397**

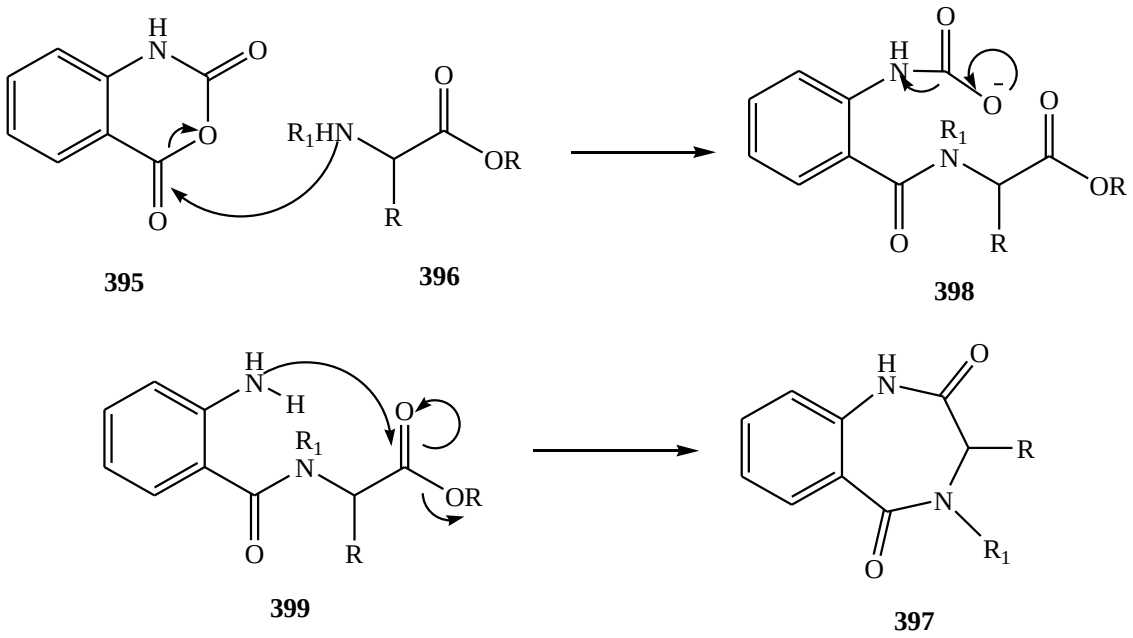
R / $R_1$= -$CH_2CH_2CH_2CH_2$ - (66%) , -$CH_2SCH_2$ - (94%)

or $R_1$ = H and R = H (79%), $CH_3$ (6%), $CH_2CH(CH_3)_2$ (66%)

Bn (57%)

**Scheme 2.78**

The mechanism of the reaction involves the nucleophilic attack of the amino group of the amino acid to the carbonyl group of isatoic anhydride followed by elimination of water and cyclisation to form the benzodiazepine ring.

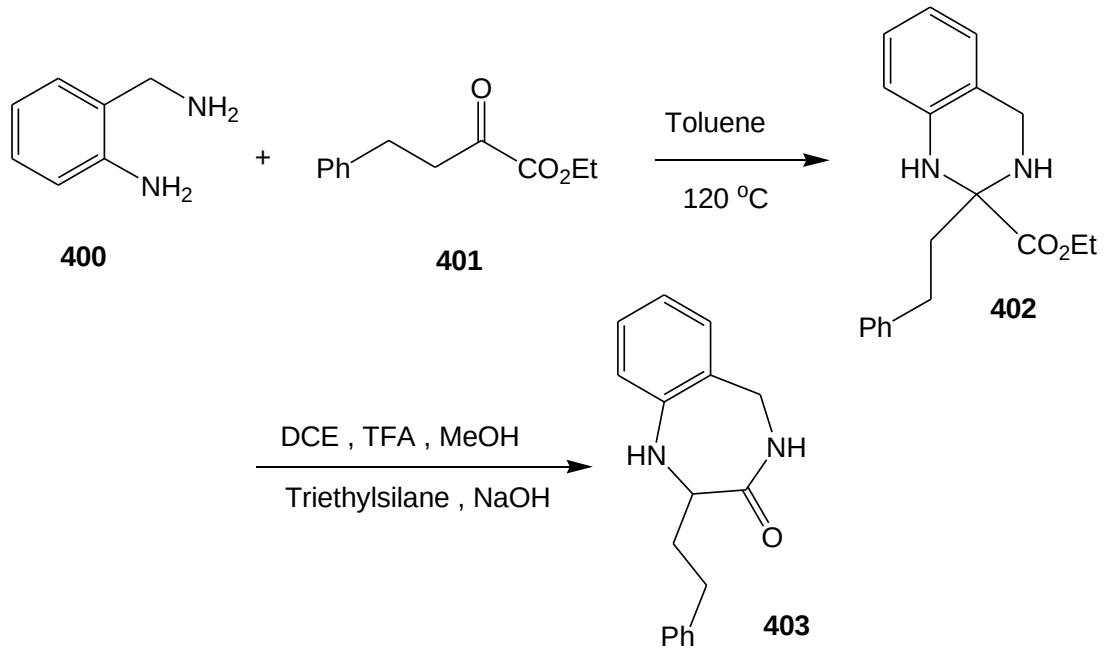


**395** **396** **398**

**399** **397**

**Scheme 2.79**

A 1,4-benzodiazepine-3-one was made from 2-aminobenzylamine which was reacted with ethyl 2-oxo-4-phenylbutyrate in refluxing toluene by using a Dean-Stark apparatus and, as a result of a condensation reaction, formed a tetrahydroquinazoline. Reduction of the quinazoline **402** with triethylsilane in TFA and 1,2-dichloroethane through the intermediate amino ester resulted in the formation of the desired 1,4-benzodiazepine-3-one **403**. It was hoped that compound **403** would be easily converted into an imine for reaction with DPP and PBD synthesis.




**400** **401** **402** **403**

**Scheme 2.80**

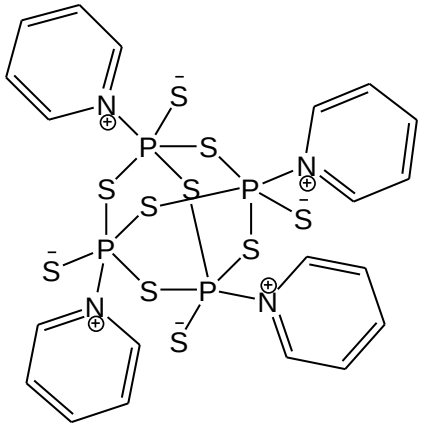
Tetrahydroquinazoline **402** formation was confirmed by spectroscopic analysis and the product was then converted into the 1,4-benzodiazepine-3-one. Spectroscopic analysis of compound **403** provided the evidence of the structure. The $^{1}H$ NMR spectroscopy showed two signals at 6.65 and 6.71 ppm to confirm two amide protons. Signals from 1.90 to 4.87 ppm confirmed the presence of four protons of the phenylethyl chain and three protons of the diazepine ring, whereas other signals showing nine aromatic protons confirmed the presence of two phenyl rings. The $^{13}C$ NMR spectrum further confirmed the structure of the product by showing a peak at 172.62 ppm for carbonyl, together with seven CH and three quaternary carbon signals between 117.65-145.43 ppm. IR and HRMS data was also consistent with the assigned structure, and all data was fully consistent with that reported in the literature[281].

## 2.5.2 Thionation of benzodiazepines

Direct *O*-alkylation was not attempted as this was the project of another student. However, these attempted *O*-alkylations were shown to lead to mixtures of *O*- & *N*-alkylated product and gave imines that were extremely unstable, either hydrolysing back to the amide or rearranging to the *N*-alkyl compound. Thioamides, however, as seen above in this work, have been shown to be easy to *S*-alkylate and form imines that are stable enough to undergo reactions. Thus, the next reaction to be explored was thiation of these benzodiazepines. A number of reagents have been developed for the thionation of amides but the most widely used method for thionation of carbonyl compounds is by using Lawessen's reagent (LR). The thionating properties of what is now called Lawesson's reagent were first studied by Schumacher[173,282] and later on its utility was brought to general attention by others[283,284]. Amongst the large number of methods used for thionation of amides are variants of LR like Davey's reagent, Belleau's reagent, Heimgartner's reagent, and fluorous variants of LR[285-289]. LR has also been used in combination with microwave and ultrasound radiations to increase its reactivity[290]. $P_4S_{10}$ has also been used with different modifications like the addition of bases e.g. $Na_2CO_3$ (Brillon's reagent), $NaHCO_3$ (Scheeren's reagent), $(TMS)_2O$, R-Li or silicon oil[286,290-297]. $P_4S_{10}$ has also been used with alumina[298,299] and silica in combination with microwave radiation[300].

Lawesson's reagent is often more selective than other reagents like $P_4S_{10}$, and is more effective in the case of primary amides because of less nitrile formation. Easy work up, commercial availability and high yields mean that it is often the preferred reagent to use for thionation of numerous species including benzodiazepines. However, we found Lawesson's reagent expensive, difficult to work-up and separate and also very smelly.

To solve this problem another thionating reagent, the $P_2S_5$-pyr. complex, was synthesized. This has been reported recently by Bergman[173] and co-workers as a very good thionating reagent which can be used with solvents like acetonitrile, pyridine and DMSO. This complex is formed by reacting $P_4S_{10}$ with refluxing pyridine to form a zwitterionic reagent. This complex has been used in past for thionation of carbonyl compounds but its structure has been recently determined by Bergman, and its use more widely discussed[301].

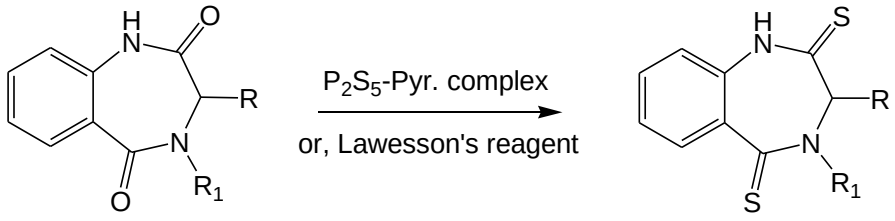


**404**

**Fig. 2.5**

This complex is particularly useful because it is inexpensive, odourless, can be used at high temperatures and is easily crystallised by lowering the temperature and filtering. It is also claimed that it can be used to do thionation selectively if there are two carbonyl groups. Thus using just 0.25 eq. of reagent in acetonitrile can give good yield of monothionated product, and using 0.5 eq. of reagent in pyridine two carbonyls can be successfully thionated when two are present. Degradation products of this complex are water soluble, so working up with water followed by filtration gives pure products, without the need for chromatographic purification.

All of the compounds in this section were thionated using either Lawesson's reagent or the Bergman reagent.




**397** **405**

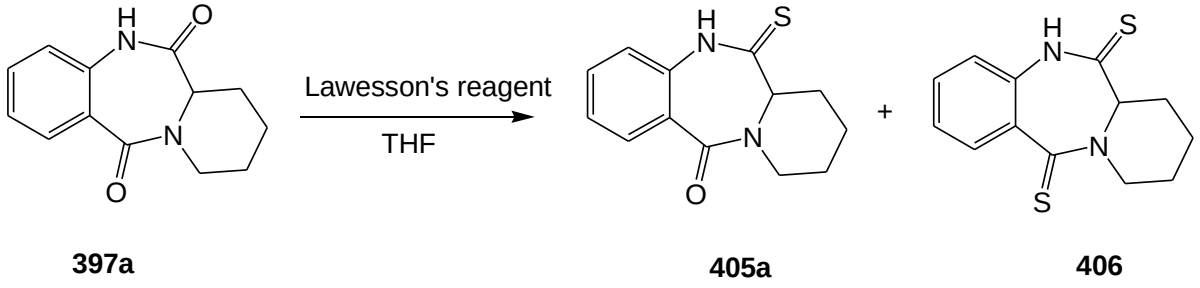
R / $R_1$= a = $-CH_2CH_2CH_2CH_2-$, b = $-CH_2SCH_2-$

or $R_1$ = H & R = c = H, d = $CH_3$,

e = $CH_2CH(CH_3)_2$ , f = Bn

**Scheme 2.81**

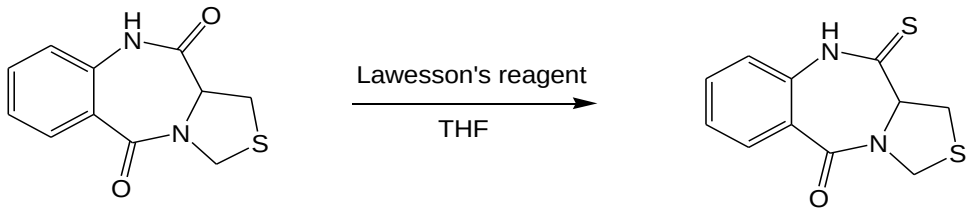
Compound **397a** was thionated using Lawesson's reagent to afford two products **405a** and **406**, one in 50 % yield as a monothionated adduct and second in 22 % yield as a dithionated adduct.




**397a** **405a** **406**

**Scheme 2.82**

The structures of the products were confirmed by spectroscopic analysis. Compound **405a** showed a broad peak in IR spectrum at 3246 $cm^{-1}$ to confirm NH whereas two peaks at 1636 and 1599 respectively infered C=O and C=S groups. A shift in absorption from 1697 to 1599 $cm^{-1}$ confirmed the thionation of one carbonyl only. In the $^{1}H$ NMR spectrum one proton of amide was confirmed by a singlet at 12.3 whereas in the $^{13}C$ NMR spectrum a shift in the peak from 171.5 to 202.18 confirmed the thionation of one carbonyl while other carbonyl appeared at 166.71. Compound **406** was confirmed as dithione by IR spectroscopy which showed shift in amide absorption of peaks from 1697 and 1636 to 1599 and 1508 $cm^{-1}$. NMR spectroscopy further confirmed the structure with two new peaks at 193.89 and 199.39 ppm in the $^{13}C$ NMR spectrum confirming the presence of two thiocarbonyls along with the loss of the two amide carbonyl signals at 168.15 & 171.50 ppm. HRMS data of both adducts **405a** and **406** was also consistent with the assigned structures. The ability of Lawesson's reagent to thionate secondary amides in preference to tertiary amides is well established[283,284]. Thionation of adduct **397b** resulted in the synthesis of the monothionated **405b** in 69 % yield as yellow solid.

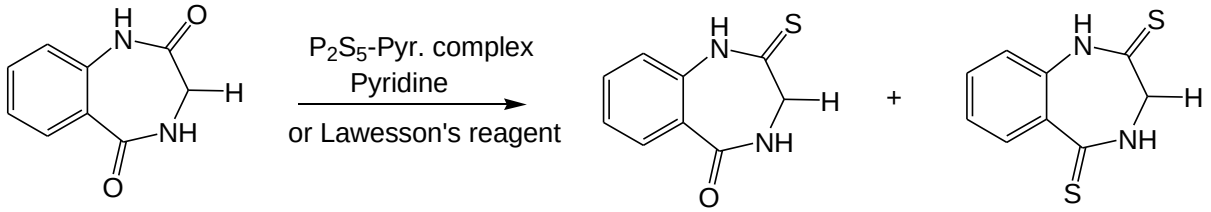



**397b** **405b**

**Scheme 2.83**

Spectroscopic analysis of the product provided the evidence for the structure of the compound **405b**. $^{1}$H NMR confirmed the structure of the product by showing an amide peak at 12.68 ppm, four aromatic protons and five aliphatic protons. $^{13}$C NMR evidenced the structure of the product with two quaternary peaks at 164.48 and 200.42 ppm to confirm the presence of one carbonyl and one thiocarbonyl. IR spectrum showed peaks with absorptions at 3430 (NH), 1701 (C=O) and 1592 cm$^{-1}$ for (C=S). HRMS further confirmed the structure of the product as the monothionated adduct.

Compound **397c** was thionated using LR in THF to afford monothionated product **405c** in 66 % yield. The IR spectrum confirmed the presence of an amide with peak at 3178 cm$^{-1}$ (NH) with carbonyl and thiocarbonyl groups 1670 and 1536 cm$^{-1}$ respectively. Amide groups were further confirmed by the $^{1}$H NMR spectrum with one peak at 8.83 ppm as a triplet with $J$ = 4.6 Hz showing its coupling with neighbouring two protons of the ring, and another peak at 12.38 ppm. A shift in one carbonyl peak was evident in $^{13}$C NMR from 171.61 to 201.27 ppm which confirms thionation of this carbonyl whereas the other carbonyl appeared at 167.29 ppm.

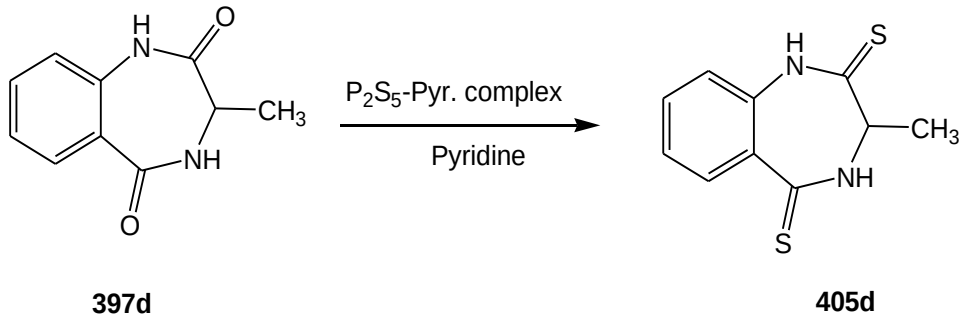



**397c** **405c** **407**

**Scheme 2.84**

In another attempt thionation of **397c** was performed by using freshly prepared $P_4S_{10}$-pyr. complex to afford compound **407** in 78 % yield as a dithione. Spectroscopic analysis evidenced for the double thionation of the starting material. Thus, the IR spectrum showed a shift in absorption of peaks from 1701 and 1670 to 1591 and 1547 cm$^{-1}$. $^{13}$C NMR confirmed two quaternary carbons at 199.70 and 196.11 ppm for two thiocarbonyls with the $^{1}$H NMR spectrum also showed a shift in amide signals from 8.55 and 10.37 to 11.14 and 12.51 ppm showing the presence of amide protons in different medium hence supporting the assigned structure of the product.

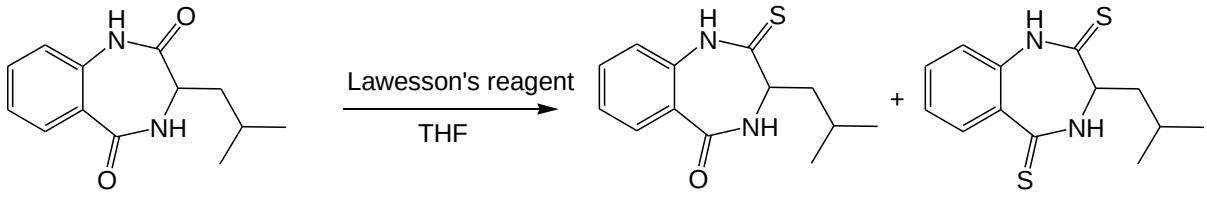
Reactivity of **397d** with $P_4S_{10}$-pyr. complex in dry pyridine afforded compound **405d** in 27 % yield as a dithione, with the expected spectroscopic characteristics.




**397d** **405d**

**Scheme 2.85**

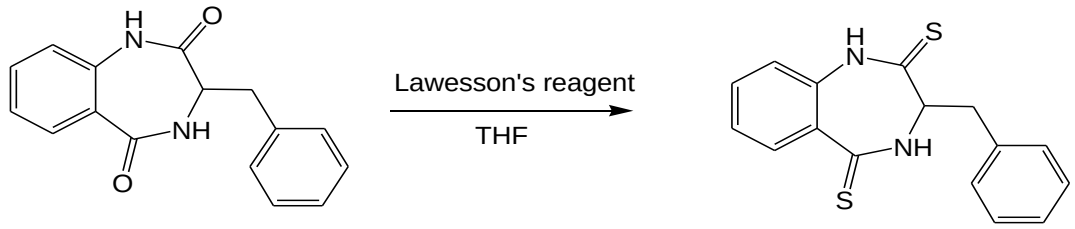
The reaction of adduct compound **397e** with $P_4S_{10}$-pyr. complex resulted in the synthesis of two products, and again the structures of both products were confirmed by NMR & IR spectroscopy as the monothione and dithione, formed in yields of 58 and 21 %, respectively.




**397e** **405e** **408**

**Scheme 2.86**

In the dithione, the two thiocarbonyls appeared at 195.31 and 201.78 ppm whereas, in the monothione, $^{13}C$ NMR spectroscopy showed two quaternary carbons at 168.22 and 204.19 ppm for the carbonyl and thiocarbonyl moieties respectively. HRMS gave the confirmation. Thionation of adduct **397f** using LR in THF afforded the compound **405f** in 97 % yield as a yellow solid.

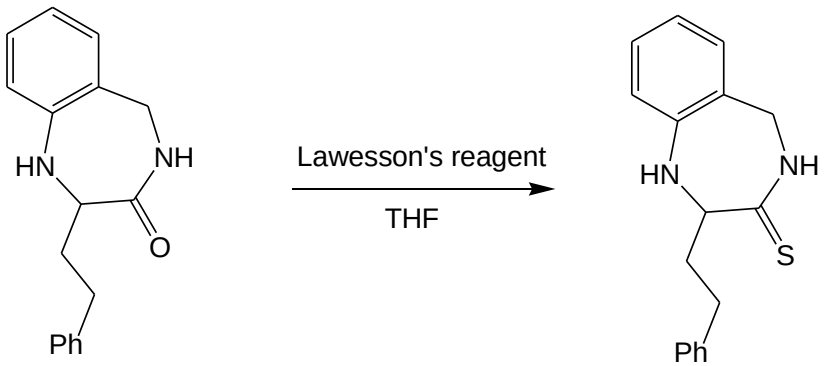



**397f** **405f**

**Scheme 2.87**

Spectroscopic analysis provided the evidence for the structure of the product with the $^{13}C$ NMR spectrum, again showing two peaks at 196.13 and 200.01 ppm for the presence of two thiocarbonyls. The IR spectrum showed a broad peak at 3169 $cm^{-1}$ for the thioamide NH groups and two peaks at 1582 and 1520 $cm^{-1}$ for the two thiocarbonyls.

Finally, compound **409** was obtained as a yellow solid in 93 % yield, as a result of thionation of adduct **403** with LR. The structure of the product was confirmed through spectroscopic analysis, although the presence of only one amide group meant that selectivity was not an issue here. The $^{1}H$ NMR spectrum showed a shift in the signal for NH to 9.06 ppm from 6.71 ppm indicating that thionation was successful. This was confirmed by $^{13}C$ NMR spectroscopy which showed a new signal at 203.43 ppm and loss of the signal at 172.62 ppm, consistent with C=O to C=S conversion. IR and HRMS confirmed the assignment. IR spectrum also showed loss of the C=O stretch.




**403** **409**

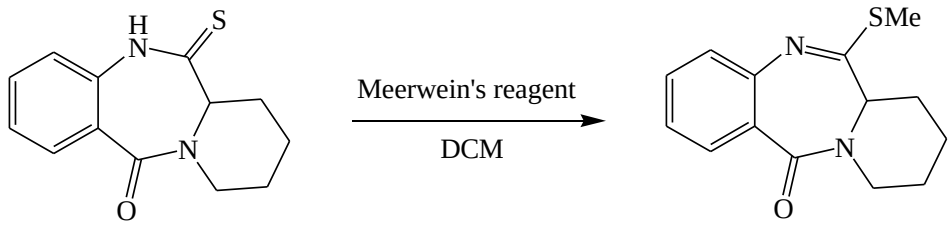
**Scheme 2.88**

No general pattern of reactivity for the thionations emerged and the process seems to be very starting material specific, at least for the benzodiazepines used here.

## 2.5.3 Alkylation of 1,4-benzodiazepine-thiones

After thionation of the benzodiazepines, the next step was S-alkylation of the adducts. It was anticipated that this would give imine or diimine functions which could be used to react with cyclopropenones and 1,3-dipoles to form fused benzodiazepines and pyrrolobenzodiazepines. Because of its success in our previous work, alkylation was done by using Meerwein's reagent in DCM and the reaction proceeded through the mechanism described before.

Alkylation of **405a** afforded the compound **410** in 56 % as yellow oil.

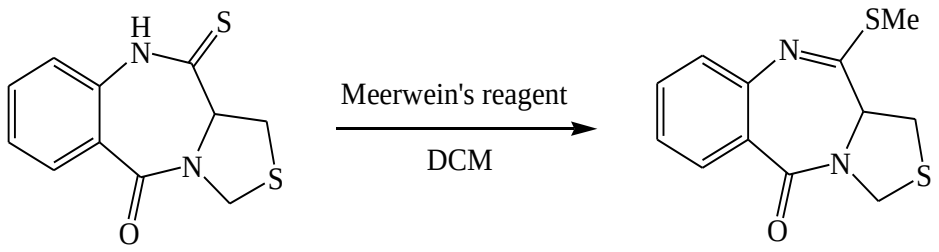



**405a** **410**

**Scheme 2.89**

The IR spectrum showed the loss of the NH peak and the emergence of a new peak at 1573 $cm^{-1}$(C=N). $^{1}H$ NMR spectroscopy confirmed the loss of an amide peak and emergence of a singlet at 2.42 ppm integrating to three protons that confirmed S-alkylation of the adduct **405a**. In the $^{13}C$ NMR spectrum a methyl peak at 13.32 ppm confirmed the presence of SMe and a new peak at 167.99 ppm confirmed the new C=N, whereas the C=S signal was missing which confirmed the successful formation of compound **410**. HRMS confirmed that methylation had occurred.

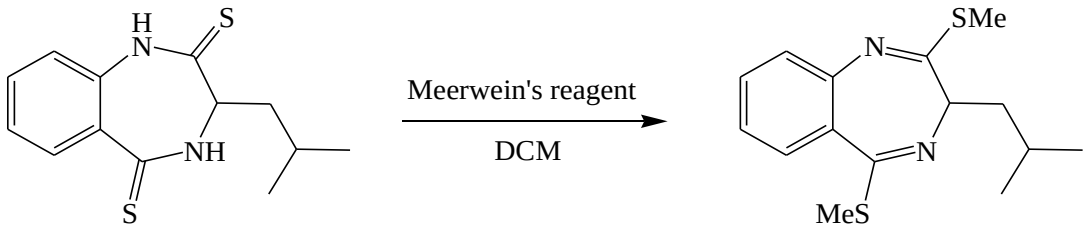
Compound **411** was obtained as a result of alkylation of **405b** in 50 % yield. The structure of the product was confirmed by spectroscopic analysis, which showed similar features to those just discussed for compound **410**.




**405b** **411**

**Scheme 2.90**

The reaction of adduct **405e** with Meerwein's reagent resulted in the double S-alkylation of adduct **405e** to form compound **412** in 69 % as a yellow oil.

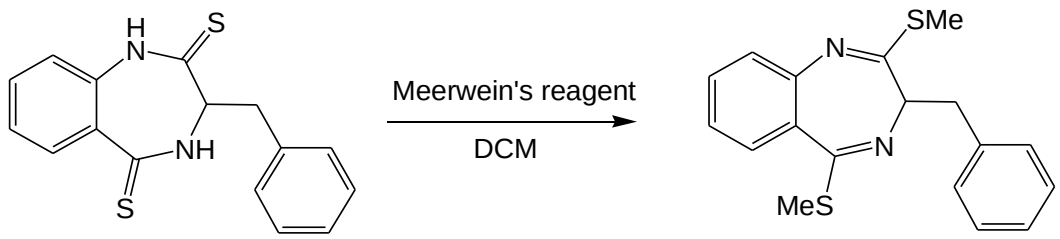



**405e** **412**

**Scheme 2.91**

Spectroscopic analysis of both products confirmed their structures. In the $^{1}$H NMR spectrum of compound **412**, two singlets appeared at 2.43 and 2.48 ppm both integrating to three protons each which confirmed the presence of two methyl groups. The $^{1}$H NMR spectrum also confirmed the loss of both amide NH peaks whereas the remaining signals confirmed the presence of the isobutyl chain and aromatic ring. In the $^{13}$C NMR spectrum, peaks for C=S were absent and two new quaternary carbon signals appeared at 166.49 and 169.63 ppm confirming the presence of the two C=N groups.

Compound **413** was produced as a yellow oil in 93 % yield as a result of alkylation of both amides in compound **405f**.

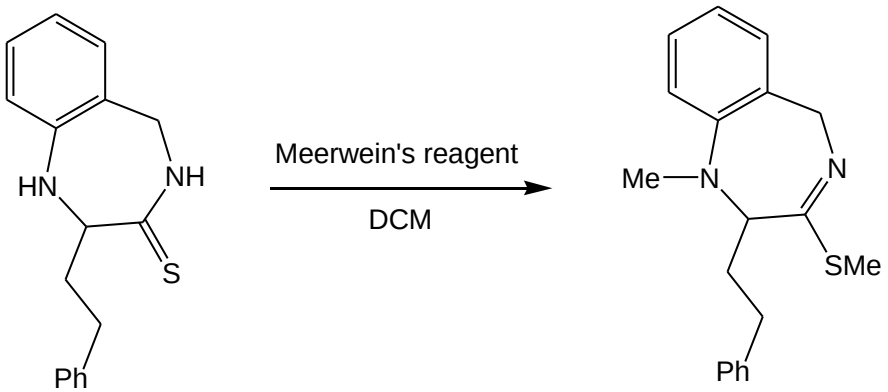



**405f** **413**

**Scheme 2.92**

Spectroscopic analysis confirmed the presence of two SMe with two singlets at 2.44 and 2.49 ppm in the $^{1}$H NMR spectrum, both integrating to three protons. $^{1}$H NMR spectroscopy also confirmed the loss of both amide protons. $^{13}$C NMR spectroscopy further confirmed the structure by showing two quaternary carbons at 166.22 and 168.23 ppm for the two new C=N carbons, whereas the two distinctive signals for C=S were missing. Two peaks at 13.40 and 14.47 ppm confirmed the presence of two thiomethyls, hence confirming the double S-alkylation of the adduct **405f**. IR and HRMS data were also consistent with the assigned structure.

Finally, alkylation of compound **409** afforded compound **414** in 60 % yield as a yellow oil.




**409** **414**

**Scheme 2.93**

Again, the $^{1}$H NMR spectrum confirmed the loss of the NH peak from 9.06 ppm and the emergence of a SMe peak as a singlet at 2.21 ppm. $^{13}$C NMR spectroscopic analysis confirmed the loss of the C=S signal and the emergence of a new quaternary carbon at 166.99

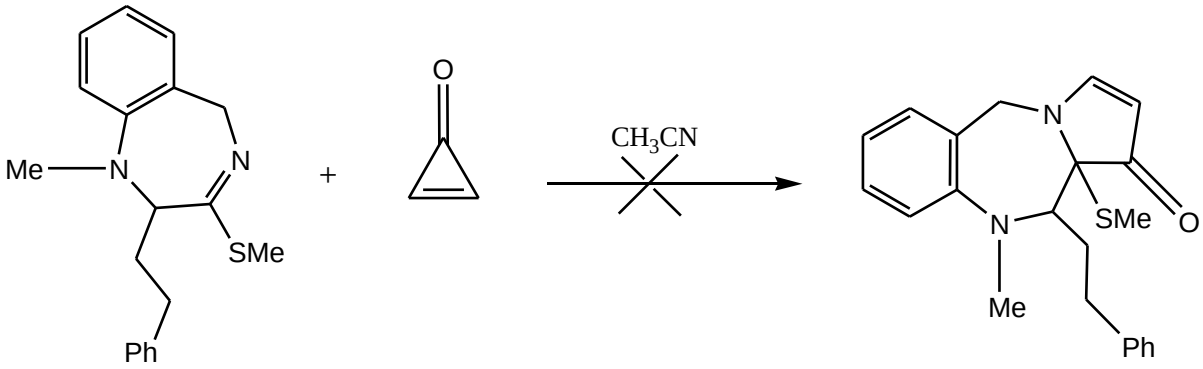
ppm to infer the presence of C=N. One signal at 12.16 ppm confirmed the presence of SMe, and all other signals were also consistent with the assigned structure.

## 2.5.4 Attempted reactivity of 1,4-benzodiazepine with cyclopropenones.

Based on the successes with other cyclic imines, it was envisaged that reaction of cyclopropenones with these cyclic imines and cyclic diimines could result in the synthesis of the pyrrolofused benzodiazepine and pyrrolobenzodiazepine heterocycles.

All attempts to react the imines **410**, **411**, **412**, **413**, **414** with diphenylcyclopropenone in various solvents at various temperatures were unsuccessful.

Finally, adducts **413** and **414** were also mixed with the parent cyclopropenone, under different conditions. For compound **414** the desired pyrrolobenzodiazepine **416** (Scheme 2.94) was not formed, with only starting material being recovered. Compound **413** was similarly unreactive.



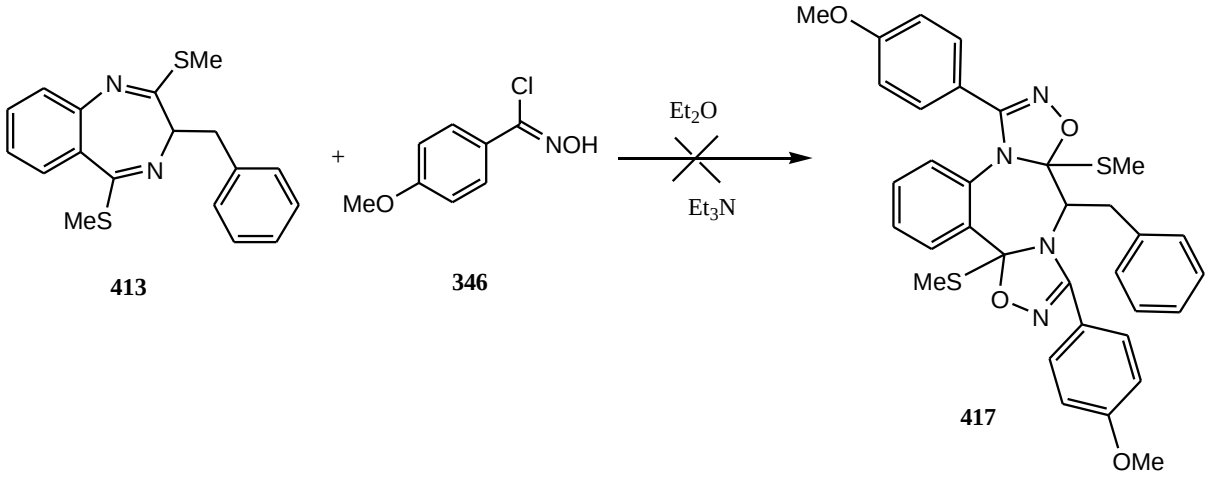

**414** **415** **416**

**Scheme 2.94**

The failure of these imines, particularly compound **414**, to react with cyclopropenones was very disappointing. However, with a route to the imines now established, we looked at their reactivity towards nitrile oxides.

## 2.5.5 Attempted reactivity of 1,4-benzodiazepine with 1,3-dipoles.

Imines **410**, **411**, **412**, **413** and **414** were already available and all were explored. Thus, for example, imine **413** was treated with *p*-methoxybenzonitrile oxide which was generated *in situ* from *p*-methoxybenzohydroximoyl chloride with the help of triethylamine (Scheme 2.96). The reaction was monitored regularly but after purification the only new product detected was the dimer of the nitrile oxide. Other nitrile oxides behaved similarly toward imine **413**, and the other imines, **410**, **411**, **412** and **414**, were found to be similarly unreactive towards nitrile oxides.

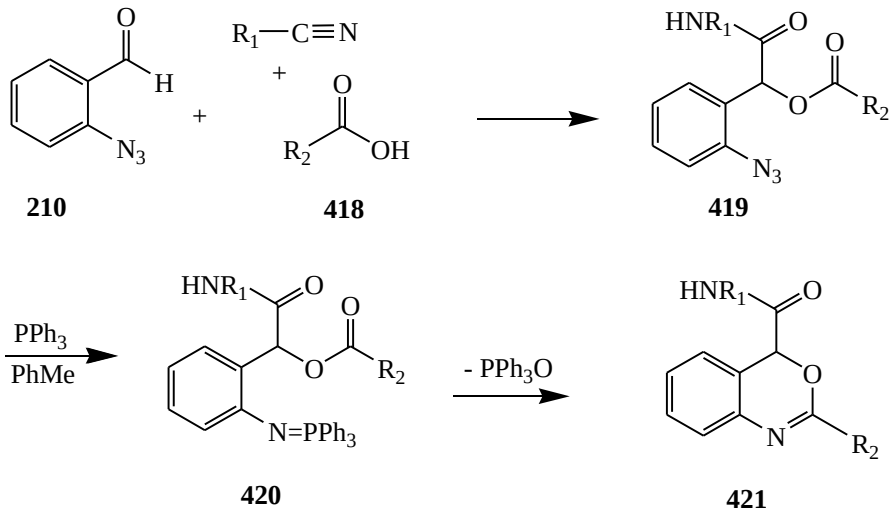



**Scheme 2.96**

## 2.6. Multicomponent reactions of *o*-azidobenzaldehyde

Multi-component reactions (MCRs) are of considerable interest in present day research due to the ability they have of making complex target molecules of biological relevance efficiently, especially in drug discovery[302]. The use of aldehydes in such reactions has also created opportunities to make combinatorial libraries of compounds and complex molecules[303]. We had a large stock of *o*-azidobenzaldehyde available (which had been used to make *o*-azidobenzonitrile oxide for previous studies in this work) and decided, in light of the disappointing results in the previous section, to explore its use as an aldehyde in multicomponent reactions.

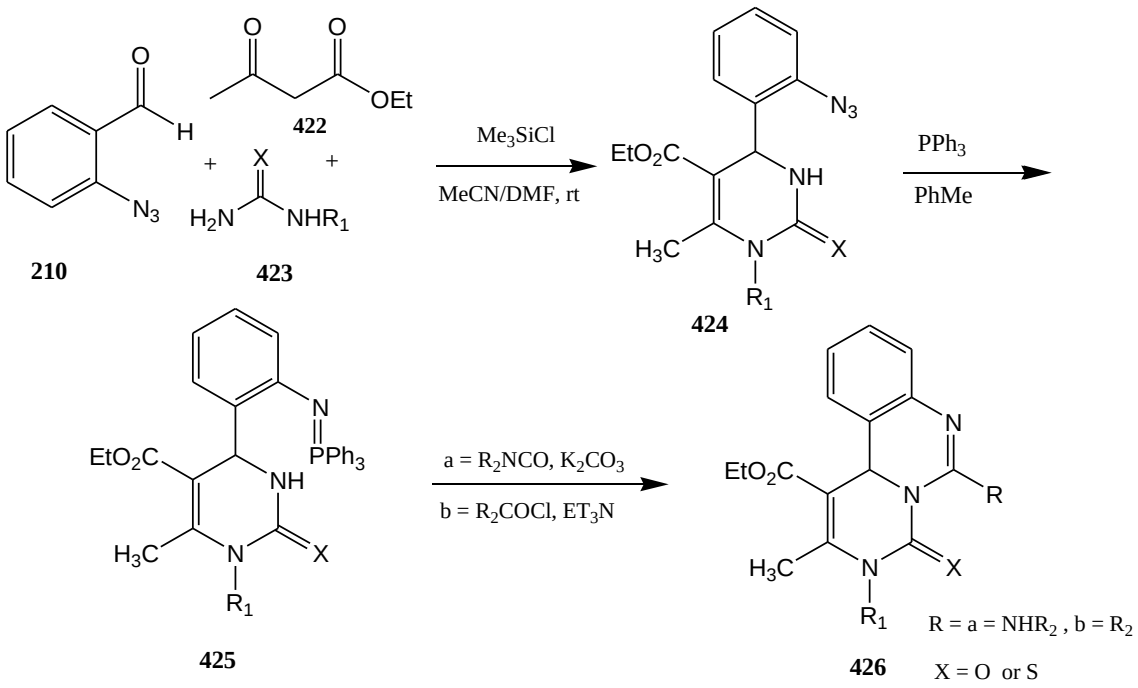
In terms of MCRs, the azide group offers an opportunity for new reactivity of the MCR products as azides have a lot of chemistry open to them[246]. The use of 2-azido benzaldehyde in multi-component reactions has begun to be explored by Ming-Wu Ding[304], where 2-azidobenzaldehyde, an isocyanide and carboxylic acids were mixed to make α-acyloxy carboxamide azides through the Passerini reaction. Subsequent Staudinger and intramolecular aza-Wittig reactions gave 4H-1,3-benzoxazines **421** (Scheme 2.97).




**Scheme 2.97**

The same group[305] also used 2-azido benzaldehyde in a Biginelli reaction (Scheme 2.98) with ethyl acetoacetate and a urea (or thiourea) to make dihydropyrimidinone azides. Again using

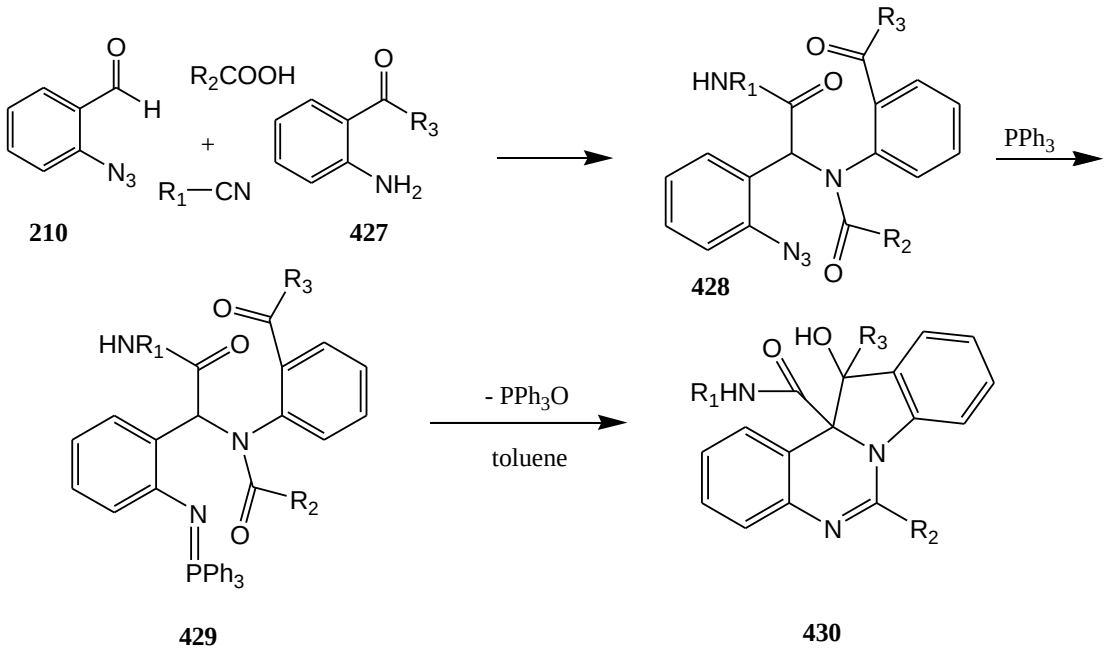
the Staudinger reaction, iminophosphoranes **425** were reacted with isocyanates, acyl chlorides or $CS_2$ in the presence of $K_2CO_3$ or $NEt_3$ to further synthesize pyrimido [1,6-c] quinazoline-4-ones **426**.




**210** **422** **423** **424** **425** **426**

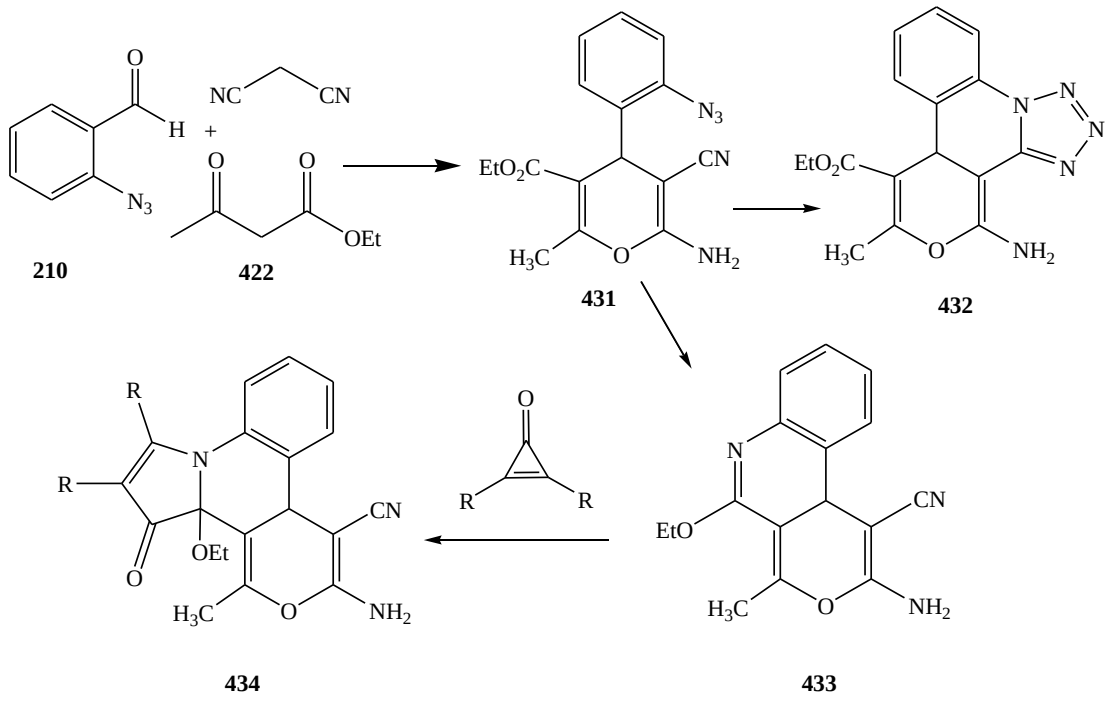
**Scheme 2.98**

2-Azido benzaldehyde has also been used in the Ugi reaction (Scheme 2.99) with a carboxylic acid, 2-acylaniline and isocyanide by the same group[306] to make azides **428** which underwent tandem Staudinger-aza-Wittig reactions to give indolo[1,2-c]quinazolines **430**.




**Scheme 2.99**

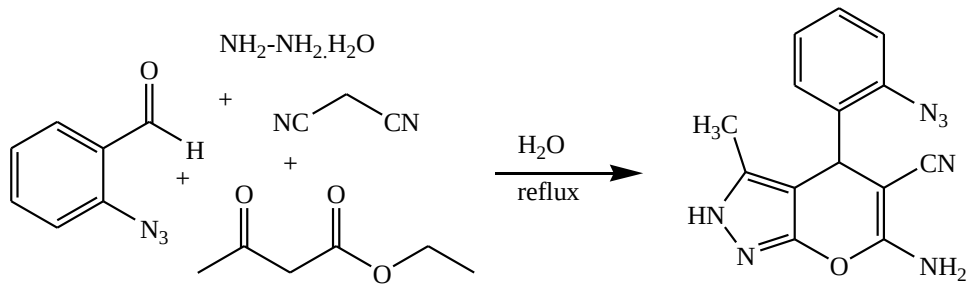
In our approach, we searched for other MCRs involving aldehydes and looked to explore the use of 2-azidobenzaldehyde in such processes. We were particularly interested in reactions that had cyano groupings present so that the possibility of azido-nitrile 1,3-dipolar reactions could be explored, as this area is unexplored in MCR processes. Secondly, we had the additional aims of using the azide to generate imines (as per Ding) but then using the imines as starting materials for the cyclopropenone type [3+2] additions discussed in previous sections. A typical example of this aim is shown in Scheme 2.100 below, and will be discussed later.



**Scheme 2.100**

### 2.6.1 Synthesis of *6-amino-4-(2-azidophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]-pyrazole-5-carbonitrile*[307].

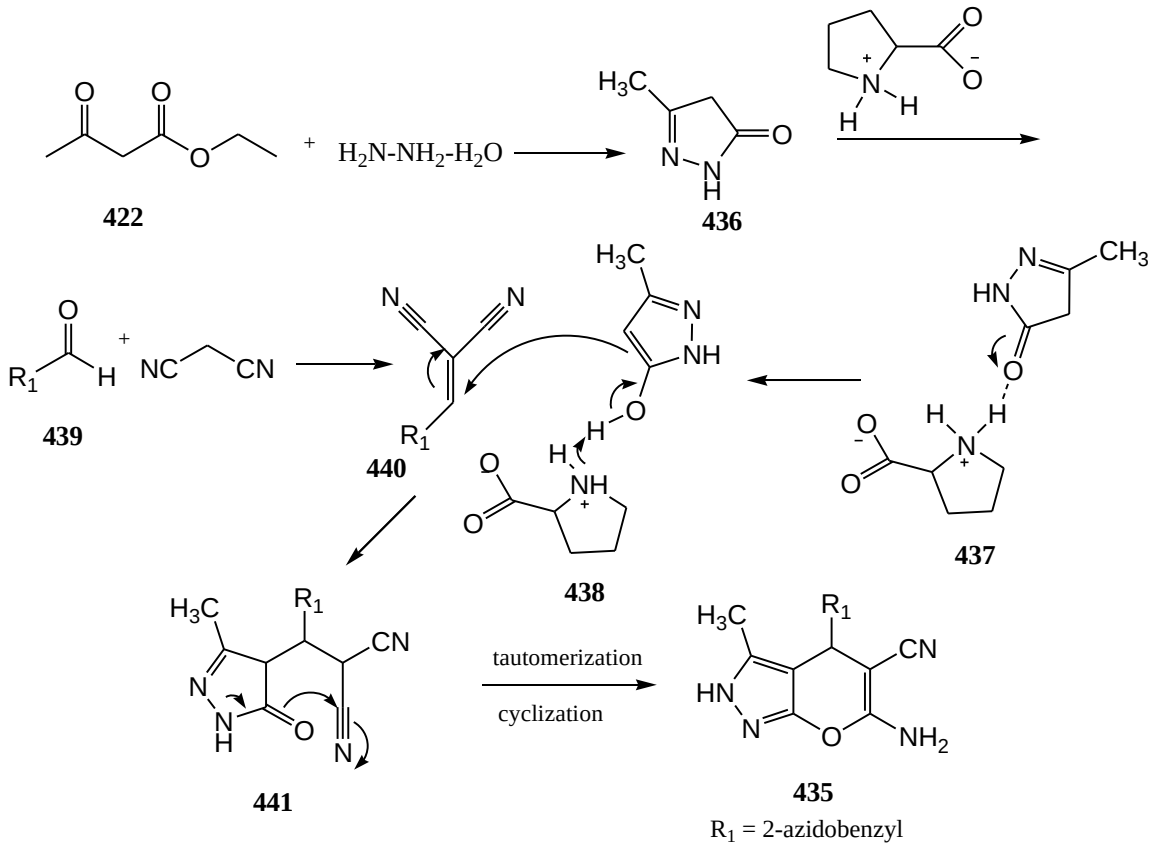
A mixture of ethyl acetoacetate (EAA), hydrazine hydrate, 2-azidobenzaldehyde and malononitrile in water was refluxed for 20 minutes in the presence of L-proline as a catalyst to get the pyrazole as a product in 41 % yield which contains one cyano group and one 2-azido benzyl as substituents at position 3 and 4 of the ring. This reaction is known with benzaldehyde[307], but had not previously been attempted with 2-azidobenzaldehyde.



**Scheme 2.101**

Spectroscopic analysis was consistent for the assigned structure of the product. The IR spectrum confirmed the presence of azide group with a strong peak at 2123 $cm^{-1}$. Nitrile and $NH_2$/NH were also seen by IR spectroscopy. The $^1H$ NMR spectroscopy confirmed the presence of one $CH_3$ with a singlet at 1.77 ppm and another singlet at 4.86 ppm showed the proton of the pyran ring. Two singlets at 6.88 and 12.15 ppm confirmed the presence of the two protons of $NH_2$ and the one proton of NH moieties, respectively. The presence of four aromatic protons confirmed the disubstituted benzene ring. In the $^{13}C$ NMR spectrum, a signal at 10.03 ppm confirmed the methyl group, with four CH and seven quaternary signals confirming the presence of the benzene ring, pyrazole and pyranyl alkene carbons. $^{13}C$ NMR data showed further peaks for the nitrile carbon and the $sp^3$ pyranyl CH group.

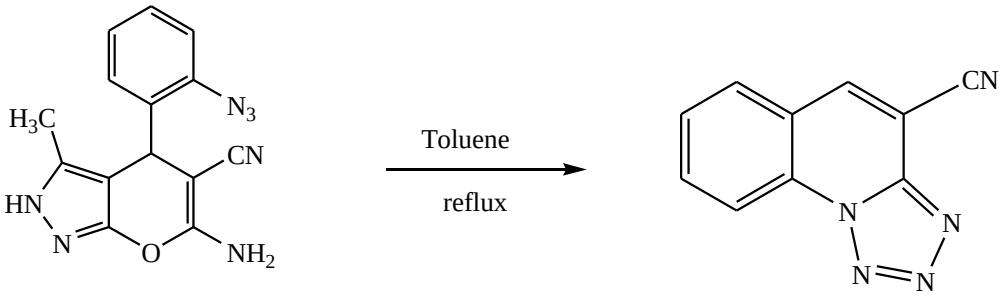
The mechanism proposed for this reaction[307] begins with pyrazole **436** formation from EAA. Ionisation of L-proline in water then facilitates the formation of an enolate from the pyrazole. The enolate attacks the Knoevenagel product **440** of *o*-azidobenzaldehyde and malononitrile, to produce the Michael adduct **441** which undergoes Thorpe-Ziegler[307] type intramolecular cyclization followed by tautomerization to give the final product **435**.




**Scheme 2.102**

### 2.6.2. Reactivity of *6-amino-4-(2-azidophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile* : Synthesis of tetrazolo[1,5-a]quinoline-4-carbonitrile.

In an attempt to achieve the intramolecular cyclization of azide and nitrile, adduct **435** was heated in refluxing toluene. After the purification the only product afforded was tetrazolo[1,5-a]quinoline-4-carbonitrile **442** in 75 % yield as a brown solid.

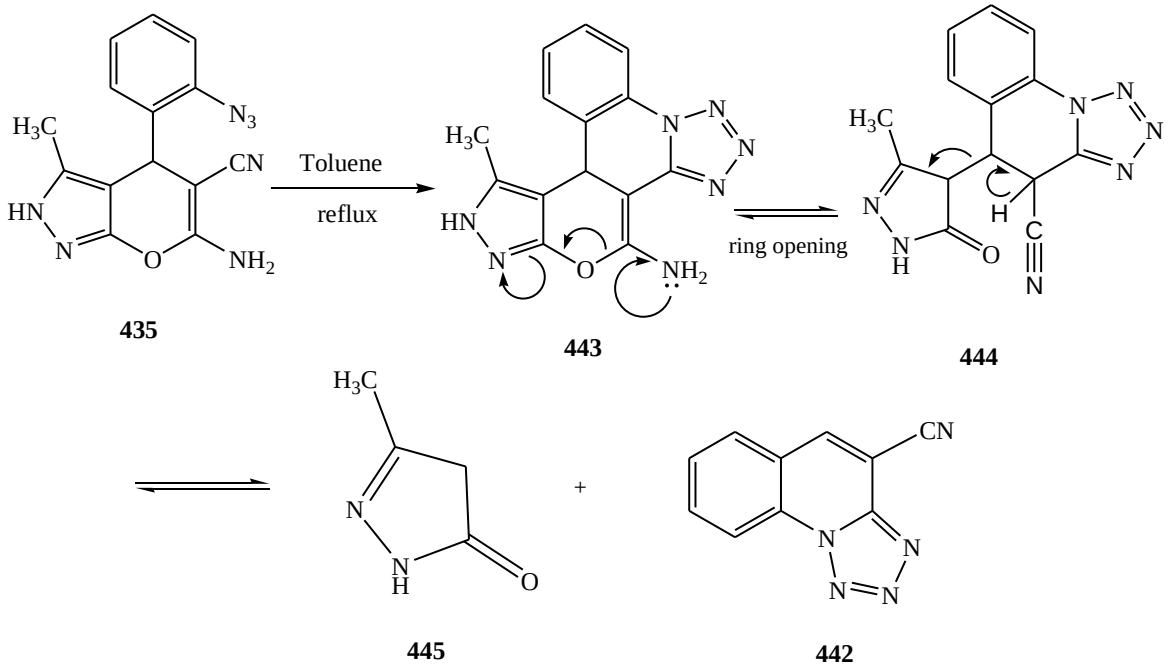



**435** **442**

**Scheme 2.103**

The structure of this product was confirmed through spectroscopic analysis. The IR spectrum confirmed the loss of azide group at 2121 $cm^{-1}$ and the presence of a nitrile group with a peak at 2242 $cm^{-1}$. $^{1}H$ NMR spectroscopy confirmed the presence of four aromatic protons and a singlet at 9.24 ppm confirmed one proton of the alkene. $^{13}C$ NMR spectroscopy showed four CH and two quaternary signals of the aromatic ring. A peak at 117.01 appeared for the CH of alkene and two quaternary carbons at 114.54 and 97.66 ppm appeared for the quaternary carbon of malononitrile and nitrile carbons, respectively. This compound is known in the literature and the data was fully consistent. MS data was also consistent with the assigned structure of the product.

It is assumed that intramolecular cyclization of azide and nitrile produced the tetrazole ring and then pyrazole ring ring enter into the reverse of the mechanism described in Scheme 2.102 to release the compound **442**.

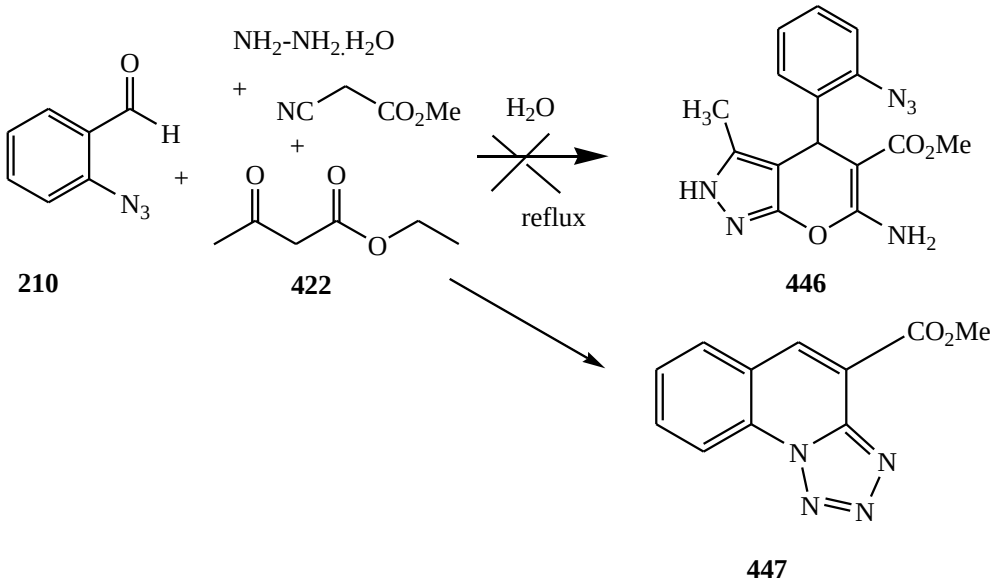



**Scheme 2.104**

### 2.6.3. Synthesis of methyl tetrazolo[1,5-a]quinoline-4-carboxylate.

Next, the same reaction was repeated with methyl cyanoacetate rather than malononitrile. Thus, a mixture of ethyl acetoacetate, hydrazine hydrate, 2-azidobenzaldehyde and methyl cyanoacetate in refluxing water in the presence of L-proline was set up. The only product that could be isolated was **447** in 19 % yield instead of the expected pyranopyrazole **446**. After purification, structure of the compound **447** was confirmed by spectroscopic techniques.

IR spectrum confirmed the absence of azide and nitrile moieties and the presence of carbonyl group was confirmed with peak 1714 $cm^{-1}$. The $^{1}H$ NMR spectrum confirmed the presence of a methoxy group with a singlet at 4.15 ppm and another singlet at 8.80 ppm confirmed one proton of alkene. The $^{13}C$ NMR spectroscopy confirmed the presence of five quaternary carbons, and five CH between 163 & 117 ppm. The signal for the methoxy group appeared at 53.04 ppm. Mass spectrometry further confirmed the structure of the product.



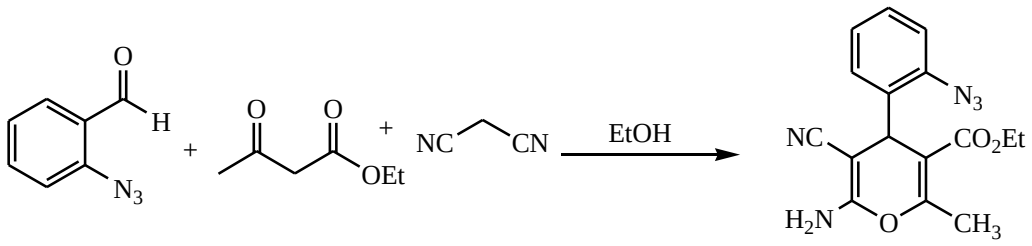

**210** **422** **446** **447**

**Scheme 2.105**

It was assumed that condensation product of aldehyde **210** and methyl cyanoacetate underwent an intramolecular azide to nitrile cyclisation to form the compound **447**, and did not react with the enolate produced from the ethyl acetoacetate, hydrazine hydrate product **436** after deprotonation by L-proline as described in Scheme 2.102. Alternatively, compound **446** might have been produced and then undergone ring opening of the pyran as described in Scheme 2.104 followed by intramolecular cyclisation of azide and nitrile moieties to form the tetrazole ring, and finally the loss of fragment **445** to give compound **447**.

### 2.6.4. Synthesis of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate.*

The reaction of 2-azidobenzaldehyde with ethyl acetoacetate and malononitrile in the presence of triethylamine afforded the product **448** in 59 % yield. The reaction was done in EtOH at room temperature and after purification, spectroscopic analysis provided the evidence for the structure of the product. When benzaldehyde was used in the original literature, the corresponding 4-phenylpyran was formed[308].



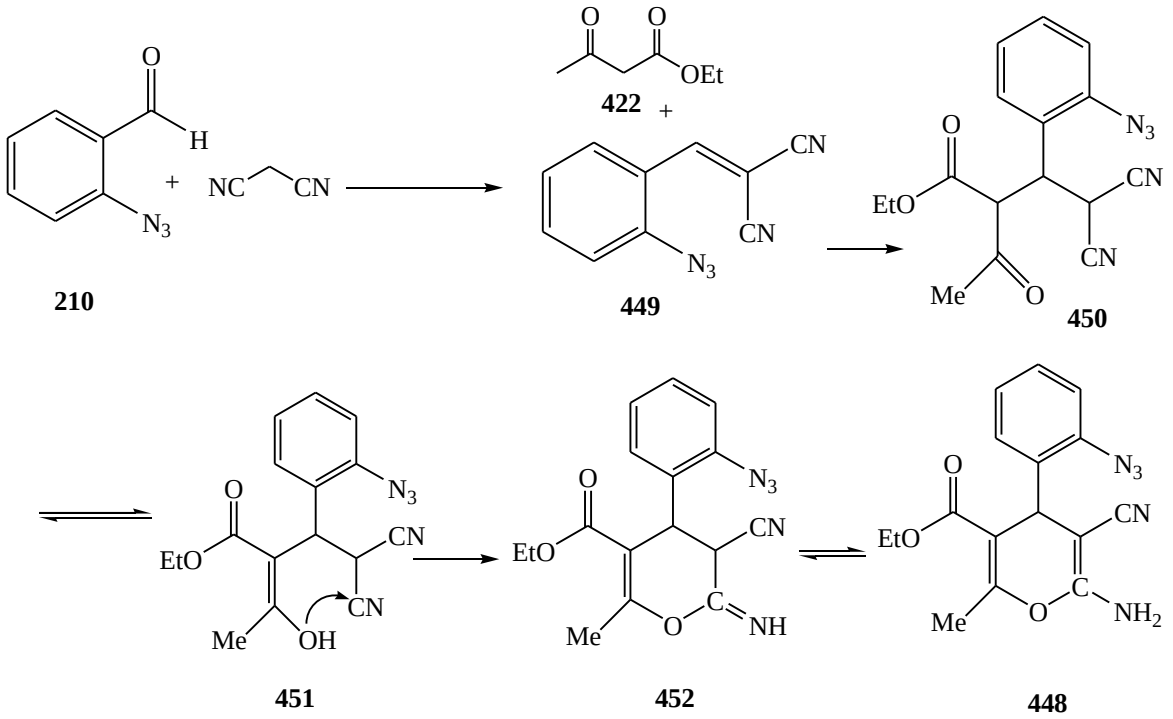

**210** **422** **448**

**Scheme 2.106**

The IR spectrum showed peaks with absorptions at 2203, 2119 and 1704 $cm^{-1}$ to confirm the presence of nitrile, azide and carbonyl moieties respectively.

$^{1}H$ NMR spectroscopy confirmed the presence of four aromatic protons and one proton of the pyran ring which appeared as a singlet at 4.79 ppm. One singlet at 4.57 confirmed the presence of two amine protons and another singlet at 2.38 ppm confirmed three methyl protons. The two $CH_2$ protons of the ethyl group appeared as a multiplet at 3.93-4.06 ppm, which together with a triplet at 1.06 ppm with a coupling constant of 7.0 Hz confirmed the presence of the ethyl chain. $^{13}C$ NMR spectroscopy showed two quaternary carbons at 165.79 and 157.84 ppm respectively for C=O and CN moieties. The ethyl group was confirmed by two signals at 33.47 and 18.45 ppm, whereas the peak for the other methyl appeared at 13.18 ppm. Mass spectrometry further confirmed the structure of the product.

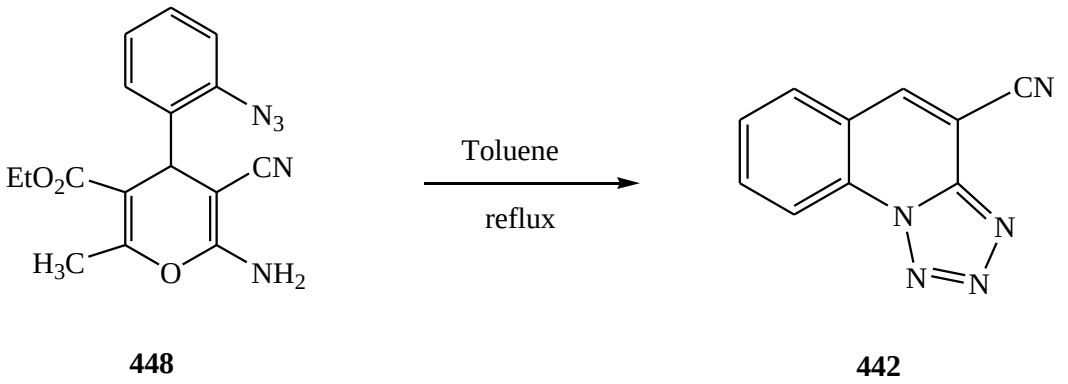
It is assumed that the reaction proceeded through a mechanism where a Knoevenagel condensation between 2-azidobenzaldehyde and malononitrile **449** produced 2-azidobenzylidene malononitrile which subsequently underwent Michael addition with ethyl acetoacetate in the presence of triethylamine leading to intermediate **450** which in turn produced the 4H-pyran **448** via the enol **451** and imine **452**, as shown in Scheme 2.107, below.



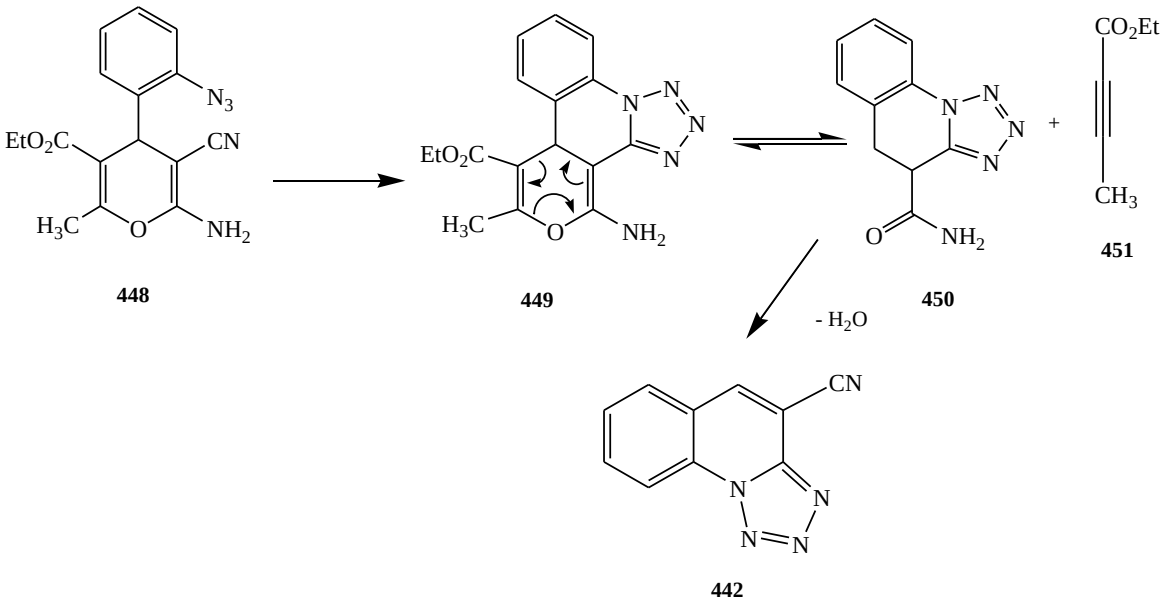

**Scheme 2.107**

### 2.6.5 Reactivity of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate.*

*Ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate* was heated in refluxing toluene in an attempt to achieve intramolecular cyclization between azide and nitrile moieties to get a tetrazole ring. After 24 hours of reflux the only product obtained in 75 % yield was characterized as tetrazolo[1,5-a]quinoline-4-carbonitrile **442** (Scheme 2.108), identical to that isolated previously, and probably forming by a similar mechanism or possibly by a retro-Diels-Alder process, as shown below, in Scheme 2.109.

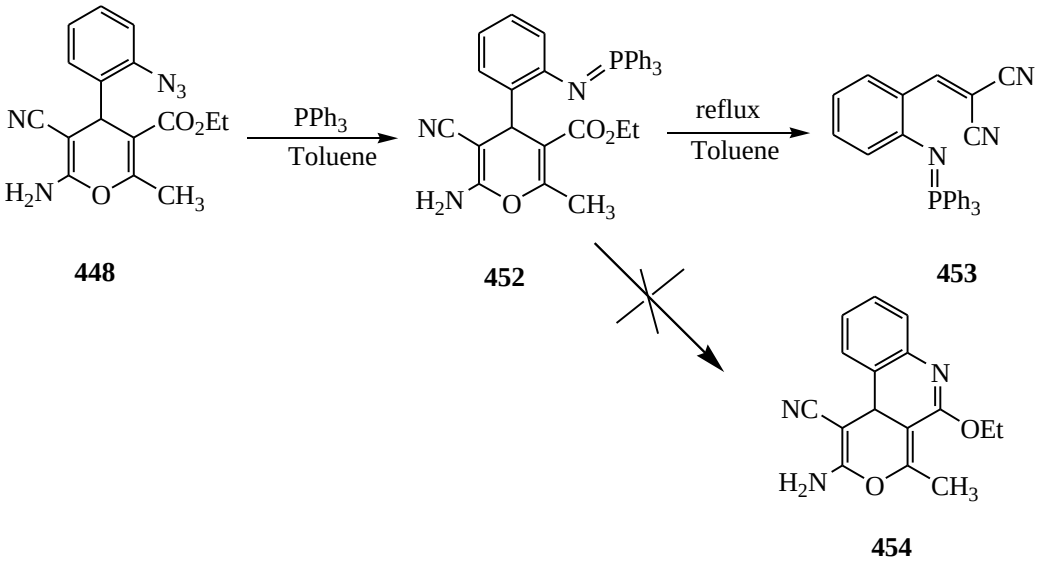



**Scheme 2.108**




**Scheme 2.109**

Having established the intramolecular 1,3-dipolar cycloaddition, it was next decided to try an intramolecular aza-Wittig reaction to try and form an imine from the azide & ester functional groups. Thus, compound **448** was reacted with triphenylphosphine at room temperature in toluene, and then at reflux in order to attempt to produce an imine **454** via aza-Wittig reaction of intermediate **452**.



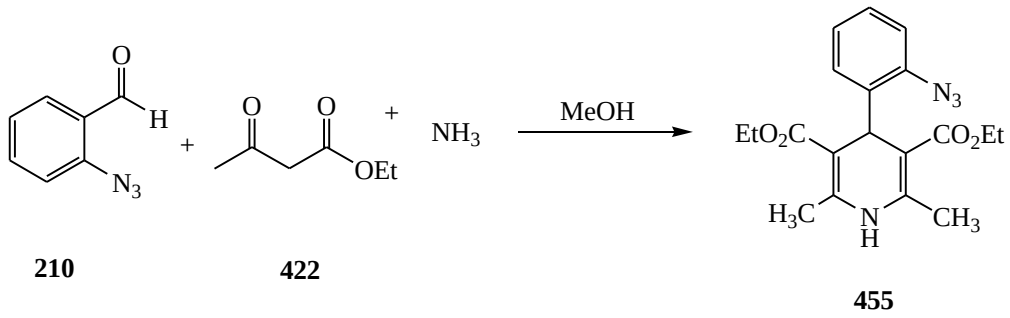

**Scheme 2.110**

After confirming the consumption of azide **448**, monitored by TLC, the reaction mixture was allowed to stir at room temperature for 12 hours (no further reaction) and then at reflux for 12

hours. The disappearance of azide **448** at room temperature is consistent with the formation of intermediate **452**, which was not isolated. Upon heating a new product was formed, which after purification and spectroscopic analysis, was assigned as compound **453** and not the desired **454**. The structure of the product **453** was confirmed by spectroscopic analysis. The $^{1}$H NMR spectrum of the product evidenced the presence of nineteen protons from 7.10 to 7.93 ppm confirming the presence of the three phenyl groups of triphenylphosphine and the one aromatic ring of the benzylidene. One singlet at 8.15 ppm showed one proton of alkene. The $^{13}$C NMR spectrum showed two quaternary carbons at 160.97 and 160.91 ppm to confirm the presence of two nitrile moieties. One CH signal at 118.94 ppm evidenced the alkene carbon of the benzylidene-malononitrile. The presence of four aromatic rings with five quaternary carbons and thirteen CH signals was also seen in the $^{13}$C NMR spectrum. IR spectrum confirmed the loss of azide from the product and mass spectrometric data further confirmed the structure of the product. It is assumed that the same type of ring opening occurs with iminophosphorane **452** as occurred with the parent **448** (see Scheme 2.109) and that similar mechanisms can be drawn, but that the absence of the azide now prevents tetrazole formation.

### 2.6.6. Synthesis of *diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.*

A mixture of 2-azidobenzaldehyde, two equivalents of ethyl acetoacetate and 20 % aqueous ammonia was mixed at room temperature to afford the compound **455** in 46 %. This is the classic Hantzsch dihydropyridine synthesis in which arylaldehyde has been used before[309] but has not been reported with 2-azidobenzaldehyde. However, previous workers did not explore subsequent attempts to react aza-Wittig imine products with cyclopropenones, which was the intention in this work.

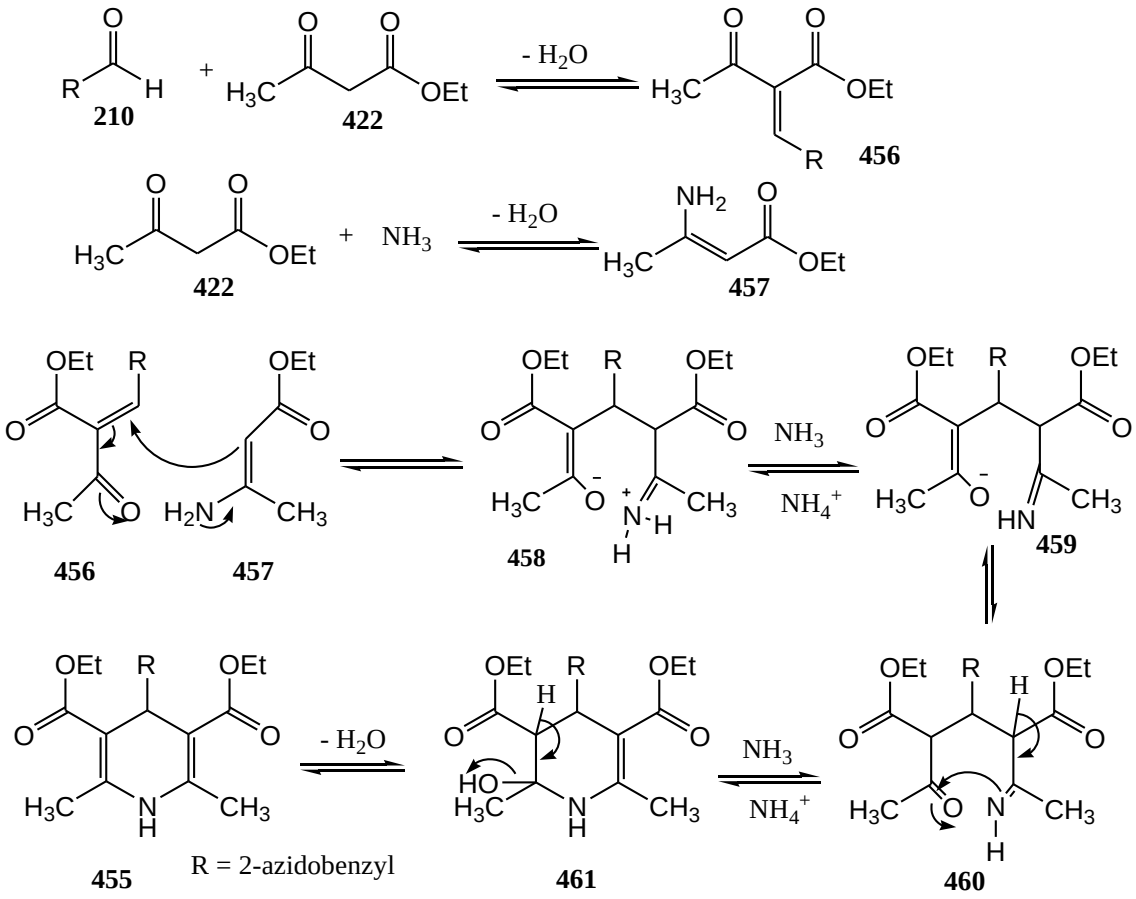



**210** **422** **455**

**Scheme 2.111**

The $^{1}H$ NMR spectrum showed a triplet at 1.20 ppm with J = 7.1 Hz, and a singlet at 2.29 ppm each integrating to six protons and each confirming the presence of the two methyls of the ester and the two methyls of the dihydropyridine ring, respectively. A multiplet at 4.08 ppm showed the four protons of two carboethoxymethylenes. The CH proton of the dihydropyridine ring appeared as a singlet at 5.18 ppm and the proton of NH appeared at 5.87 ppm as a singlet. The presence of four aromatic protons provided evidence for the azidoaryl substituent. All other data was fully consistent with the assigned structure and with previously reported data.

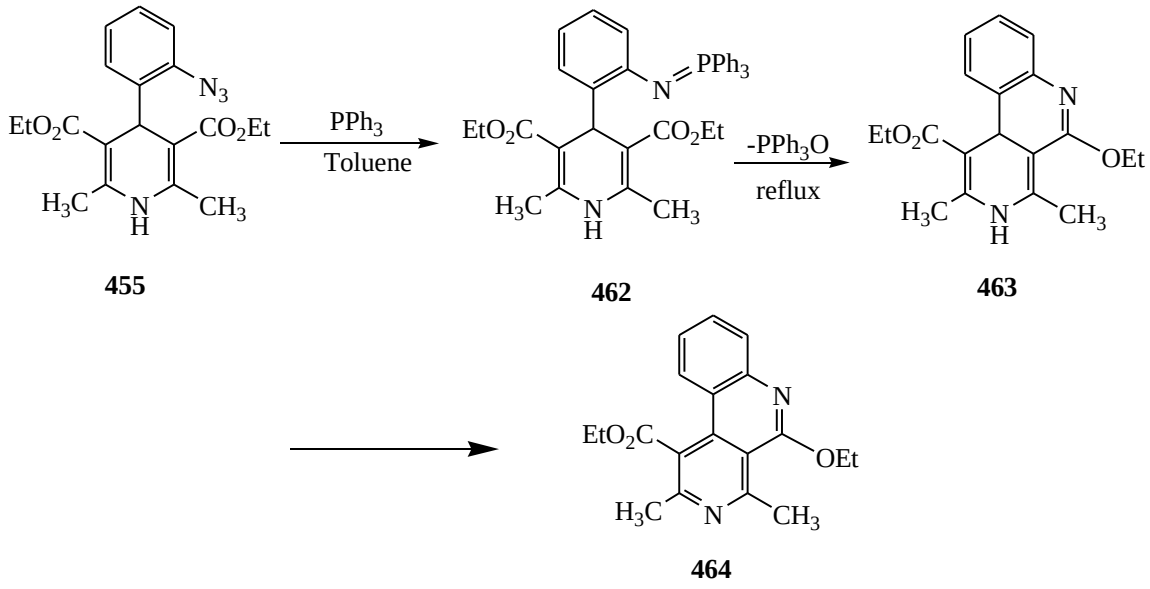
The reaction occurred according to the classic dihydropyridine synthesis mechanism described by Hantzsch. A Knoevenagel condensation of aldehyde and ethyl acetoacetate produced an intermediate and another intermediate produced by ammonia and ethyl acetoacetate underwent Michael addition followed by cyclization and tautomerization to form the product, as shown below in Scheme 2.112.




**Scheme 2.112**

*Diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate* **455** was reacted with triphenylphosphine at room temperature to form the iminophosphorane and then at reflux in a sequence of Staudinger-aza-Wittig reactions to afford compound **464** in 53 % yield. The reaction was monitored by TLC at regular intervals to confirm the formation of iminophosphorane followed by elimination of triphenylphosphine oxide to form the product.

Spectroscopic analysis provided the evidence for the structure of the product, which was in fact found to be pyridine **464**, the aromatised version of the expected dihydropyridine **463**-aromatisation must be easy in such highly conjugated systems. IR spectrum confirmed the loss of azide and a signal at 1714 $cm^{-1}$ confirmed the presence of a carbonyl of the other ester.




**455** **462** **463** **464**

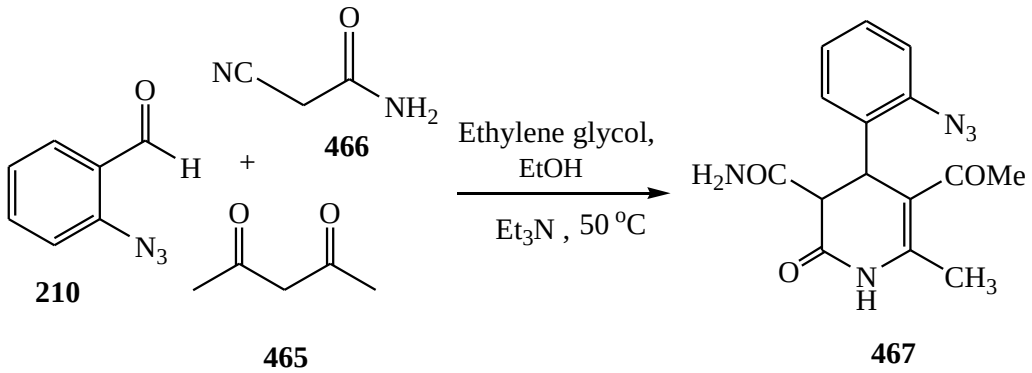
**Scheme 2.113**

The $^{1}H$ NMR spectrum showed two triplets at 1.39 and 1.54 ppm with $J$ = 7.2 and 7.0 Hz respectively to confirm two methyls of the carboethoxy and ethoxy moieties. Two singlets at 2.70 and 3.13 ppm confirmed the two other methyl substituents. Two quartets at 4.53 and 4.65 ppm with coupling constants of 7.0 Hz confirmed the presence of the two methylenes of ethyl moieties. The remaining signals confirmed four aromatic protons. The $^{13}C$ NMR spectrum agreed with the assigned structure by showing eight signals for quaternary carbons and four CH signals for the carbons of the three rings. The CH at C-4 in dihydropyridine **463** was not seen. The peak for the carbonyl appeared at 170.91 ppm and four methyl peaks and two methylene signals confirmed the structure of the product. Mass spectrometric data was

also consistent with the assigned structure, again showing that the product was the aromatised **464** and not the initially formed **463**. Unsurprisingly, the stable aromatic compound **464** showed no reactivity towards cyclopropenones.

### 2.6.7 Synthesis of *5-acetyl-4-(2-azidophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxamide.*

The reaction of *o*-azidobenzaldehyde with acetylacetone and cyanoacetamide in the presence of triethylamine afforded the compound **467** in 65 % yield as yellow oil. Again this reaction is known with benzaldehyde[310], but has not been reported with 2-azidobenzaldehyde.

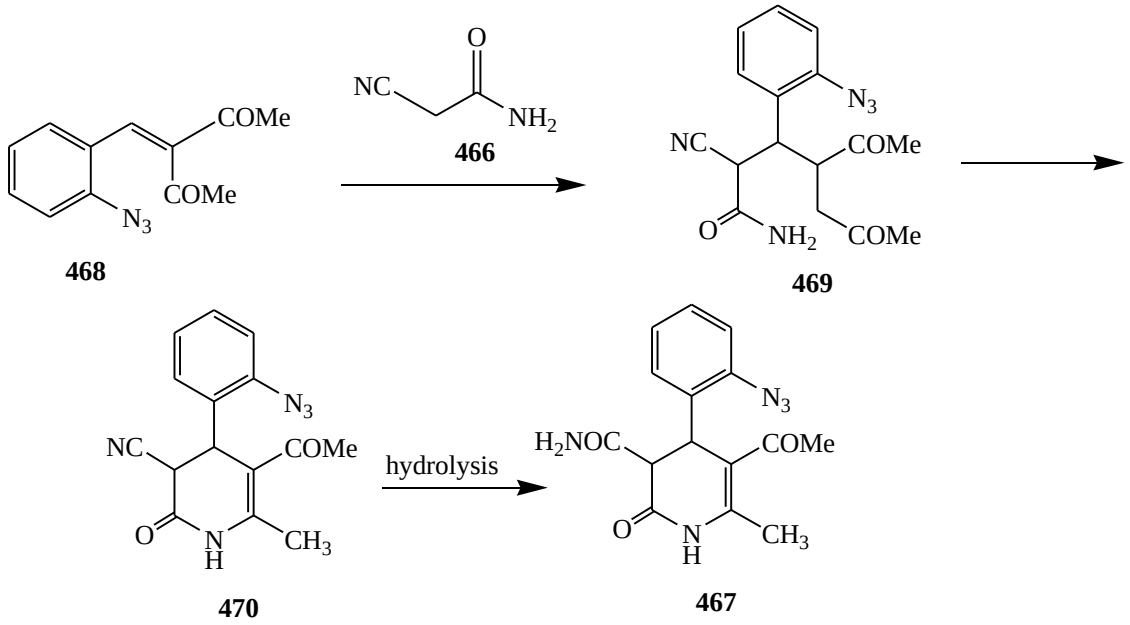



**Scheme 2.114**

The structure of the product was confirmed using spectroscopic techniques. The $^{1}$H NMR spectrum showed two singlets at 1.99 and 2.20 ppm integrating to three protons each confirming the presence of two methyl moieties. Two broad singlets at 3.26 and 4.58 ppm, respectively confirmed the two CH protons of the pyridinone ring. The three amide protons appeared as three different singlets at 7.22, 7.29 and 10.06 ppm. The presence of four aromatic protons completed the assignment of the structure of the product. The $^{13}$C NMR spectrum showed three carbonyl signals at 196.82, 168.80 and 167.45 ppm. The aromatic ring was confirmed by the presence of two quaternary and four CH signals. The two quaternary carbons of the pyridinone ring appeared at 147.58 and 137.57 ppm whereas the two CHs of pyridinone ring appeared at 54.00 and 37.45 ppm. The presence of two methyls was confirmed with two signals at 19.14 and 30.03 ppm.

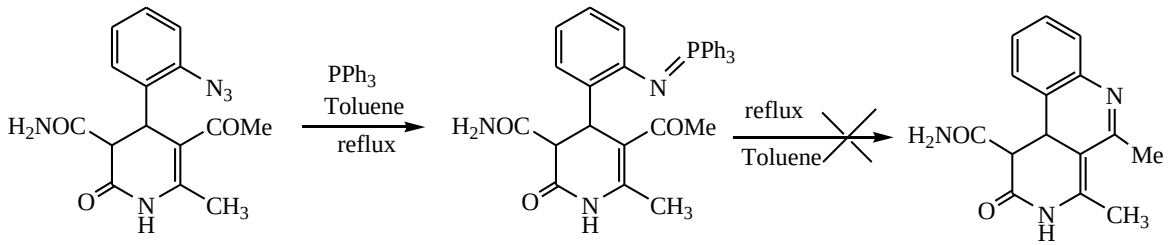
The IR spectrum confirmed the presence of azide and carbonyl moieties and mass spectrometric data was also in accordance with the assigned structure of the product.

Mechanistically, this reaction occurred following the same type of route as described above where a Knoevenagel condensation between 2-azidobenzaldehyde and acetylacetone produced an intermediate **468** which underwent a nucleophilic attack from cyanoacetamide which is a Michael donor, followed by intramolecular cyclization of the Michael adduct **469** through a nucleophilic attack of $NH_2$ on the carbonyl group of acetylacetone, and loss of water. Hydrolysis of compound **470** resulted in the synthesis of product **467**. The presence of EtOH in the reaction mixture may have caused the conversion of the nitrile to amide via oxidative hydration[311] or the nitrile may have been converted to the amide by the presence of water[312,313].




**Scheme 2.115**

As one goal of this project was to attempt intramolecular azide-nitrile cyclization or a Staudinger-aza-Wittig reaction to investigate the reactivity of MCR products, adduct **467** was reacted with triphenylphosphine at room temperature in toluene to form the Staudinger product **471** which was generated *in situ* and was then reacted at higher temperature to attempt aza-Wittig reaction between iminophosphorane and carbonyl group to form a new cyclic imine **472**, whose reactivity, towards cyclopropenones could then be explored.



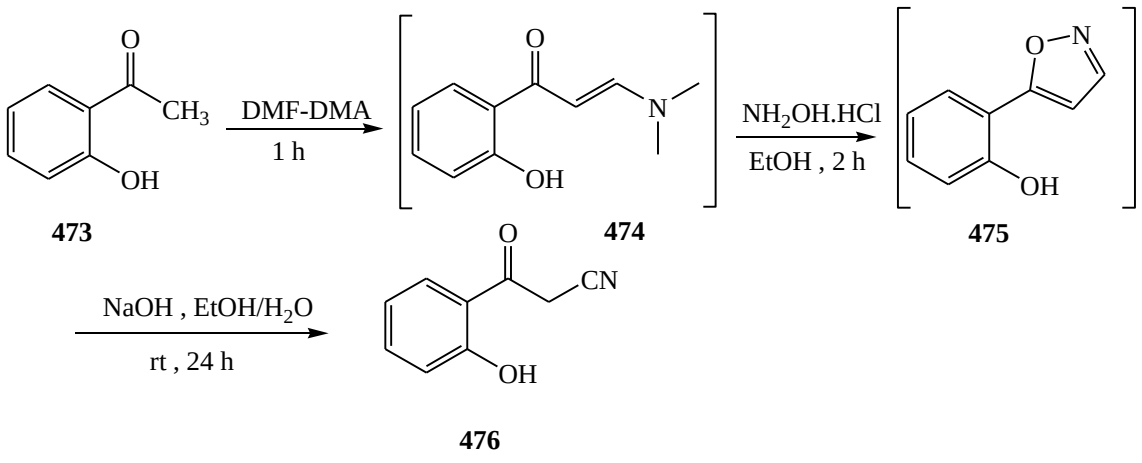

**467** **471** **472**

**Scheme 2.116**

Formation of iminophosphorane **471** was inferred by TLC showing loss of azide and so the reaction was continued on to reflux. After a few hours it was observed that adduct **471** had been decomposed without forming any single product. The TLC showed a multi-spot reaction which indicated widespread degradation. No products could be isolated from this reaction mixture.

### 2.6.8. Synthesis of 2-(2-azidophenyl)-4-oxochroman-3-carbonitrile.

3-(2-Hydroxyphenyl)-3-oxopropanenitrile **476** (Scheme 2.118) reacts with benzaldehyde to form chromanes substituted with nitriles[314]. We hoped to turn this into an MCR by using an azide which would form a tetrazole with the nitrile. 3-(2-Hydroxyphenyl)-3-oxopropanenitrile **476** and 2-azidobenzaldehyde **210** in ethanol in the presence of a small amount of piperidine afforded 2-(2-azidophenyl)-4-oxochroman-3-carbonitrile **477** in 27 % yield as shown in Scheme 2.118. 3-(2-Hydroxyphenyl)-3-oxopropanenitrile **476** was synthesized from 2-hydroxyacetophenone **473**, as shown in Scheme 2.117 below.



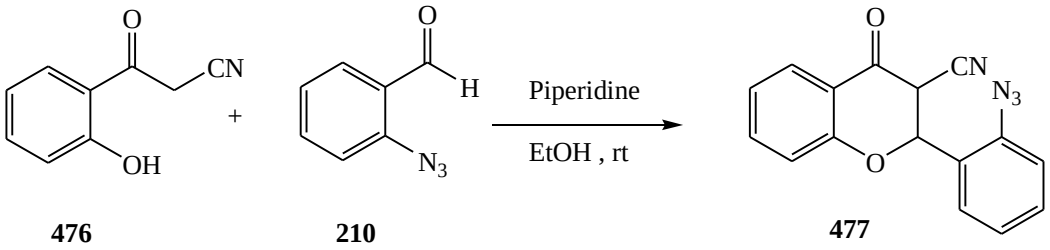

**473** **474** **475**

**476**

**Scheme 2.117**

In the first step, 2-hydroxyacetophenone **473** was converted into the corresponding dimethylamino methylene **474** as a result of condensation with DMF-DMA. Reaction of the adduct **474** with hydroxylamine hydrochloride in refluxing EtOH produced 2-hydroxyphenyl-isoxazole **475** which underwent ring cleavage upon treatment with aqueous-ethanolic NaOH solution at room temperature to give product **476** in 30 % overall yield. The structure of the adduct **476** was confirmed by NMR spectroscopy, and by comparison to the known literature data[314].

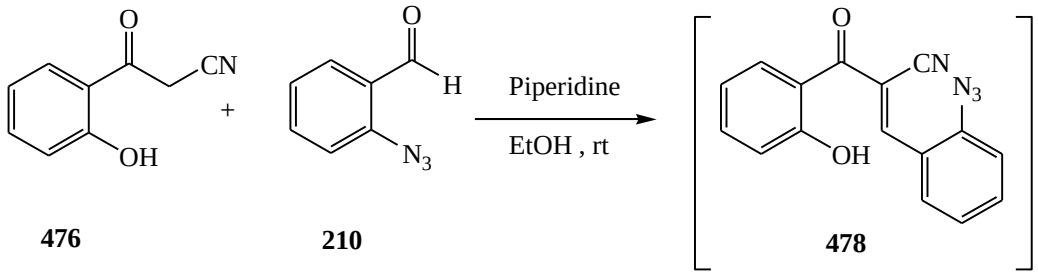
The reaction of compound **476** with 2-azidobenzaldehyde gave the desired product **477** as a mixture of diastereoisomers. Azide to nitrile cycloaddition clearly had not occurred.




**476** **210** **477**

**Scheme 2.118**

Mechanistically, compound **477** would be the product of the cyclisation of intermediate **478**, where intermediate **478** forms from the condensation of the oxopropanenitrile **476** with 2-azidobenzaldehyde as shown below.




**476** **210** **478**

**Scheme 2.119**

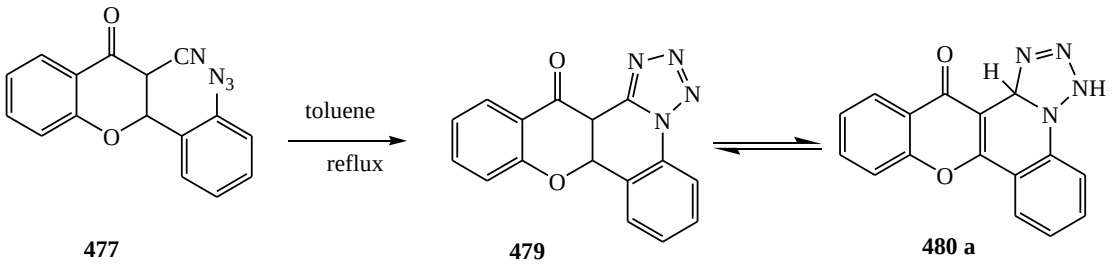
Spectroscopic analysis provided evidence for the structure of the product **477**. The IR spectrum confirmed the presence of nitrile, azide and carbonyl moieties with peaks showing absorptions at 2243, 2123 and 1700 $cm^{-1}$, respectively. The $^{1}H$ NMR spectrum showed sixteen aromatic protons confirming the product as a mixture of diastereoisomers. The two protons of the chromone ring appeared as two different sets of doublets. One set of doublets

appeared at 5.86 and 5.75 ppm with coupling constants of 12.2 and 2.4 Hz respectively, and the other set of doublets appeared at 4.42 and 3.99 ppm with coupling constants of 12.2 and 2.6 Hz, respectively, confirming that the product was a mixture of diastereoisomers.

The $^{13}C$ NMR spectroscopy further confirmed the product as a mixture of diastereoisomers by showing every signal doubled. It showed the two $sp^2$ carbons of the chromone ring as four signals at 43.37, 45.86, 74.57 and 76.05 ppm, and two quaternary carbons at 112.69 and 112.91 ppm for the two CN moieties. All the aromatic signals were doubled; finally, two peaks at 182.17 and 182.62 ppm appeared for the carbonyl moiety.

### 2.6.9. Reactivity of *2-(2-azidophenyl)-4-oxochroman-3-carbonitrile*.

2-(2-Azidophenyl)-4-oxochroman-3-carbonitrile was heated in refluxing toluene to afford the product **480a** in 65 % yield as a result of intramolecular cyclization of azide and nitrile moieties to form a tetrazole ring. The expected product **479** was not isolated, but instead its presumably more stable tautomer **480a** was isolated.




**477** **479** **480 a**

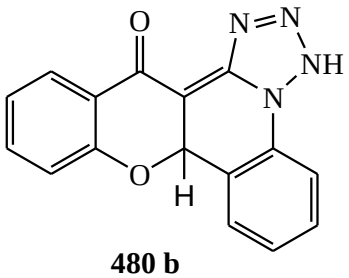
**Scheme 2.120**

The structure of the product was confirmed through spectroscopic analysis. The IR spectrum showed the loss of azide and nitrile peaks and confirmed the presence of an NH and carbonyl moieties. The $^{1}H$ NMR spectrum showed one broad singlet at 11.78 ppm to confirm one proton of NH and another singlet at 8.22 ppm showing the one proton of CH of the tetrazole ring. It has been deshielded probably because of being in a highly conjugated system and in a tetrazole ring. Other signals confirmed the presence of the eight aromatic protons of the two phenyl rings.

The $^{13}C$ NMR spectrum further confirmed the structure by showing a peak at 195.00 ppm to confirm the carbonyl group whereas the CH of the tetrazole ring appeared at 117.17 ppm.

The two quaternary carbons of the chromone ring appear at 145.85 and 163.60 ppm. The four quaternary and eight CH carbons of aromatic rings confirmed the structure of the product. Mass spectrometric data was also consistent with the assigned structure.

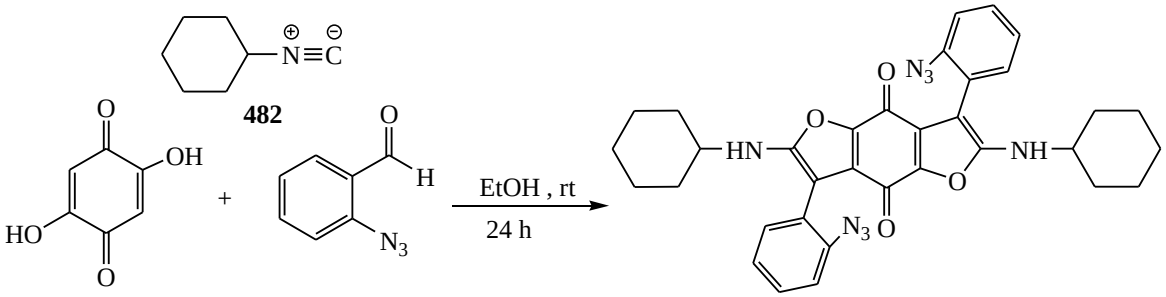
The reaction mechanism is a straightforward [2+3] cycloaddition of azide to nitrile to form a five membered tetrazole ring. The tautomerisation is presumably driven by the extra conjugation that is allowed in isomer **480a** compared to **479**. Tetrazoles of this type are known in the literature and have remarkably deshielded CHs in NMR spectroscopy. At this stage we are unable to discant compound **480b** as a possible product.



**480 b**

### 2.6.10. Synthesis of 2,6-bis (cyclohexylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione.

2,5-Dihydroxycyclohexa-2,5-diene-1,4-dione was reacted with 2-azidobenzaldehyde and cyclohexyl isocyanide to form the compound **483** (Scheme 2.121) in 13 % as a dark brown oil, again a reaction that was known to work with benzaldehyde[315] but had never been attempted with 2-azidobenzaldehyde.

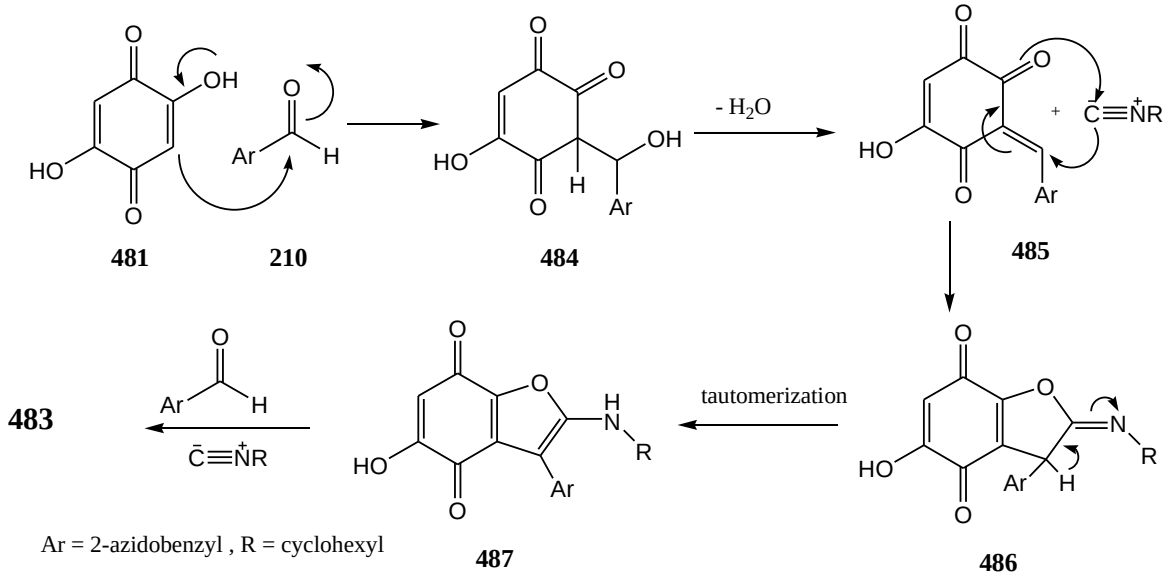



**482** **481** **210** **483**

**Scheme 2.121**

Spectroscopic analysis provided the evidence for the proposed structure of the product which is assigned tentatively and may not be correct because it is difficult to get full data[315] of compounds like **483**. The $^{1}H$ NMR spectrum of compound **483** showed twentytwo protons for two cyclohexyl rings as a series of multiplets between 1.06 to 3.75 ppm. Two amide protons appeared as doublets at 6.38 ppm with a coupling constant of 7.5 Hz. The remaining signals confirmed the presence of two aromatic rings. $^{13}C$ NMR spectroscopy confirmed the presence of two cyclohexyl rings with five signals for $CH_2$s and one for the aliphatic CH carbon, whereas the presence of four CH and seven quaternary carbons in the aromatic region confirmed the structure of the (symmetric) product. Although the $^{13}C$ spectrum was complicated by lack of solubility and NMR invisibility seen in quinones. The IR spectrum confirmed the presence of NH showing an absorption at 3521 $cm^{-1}$. Azide and carbonyl moieties showed absorptions at 2124 and 1739 $cm^{-1}$, respectively.

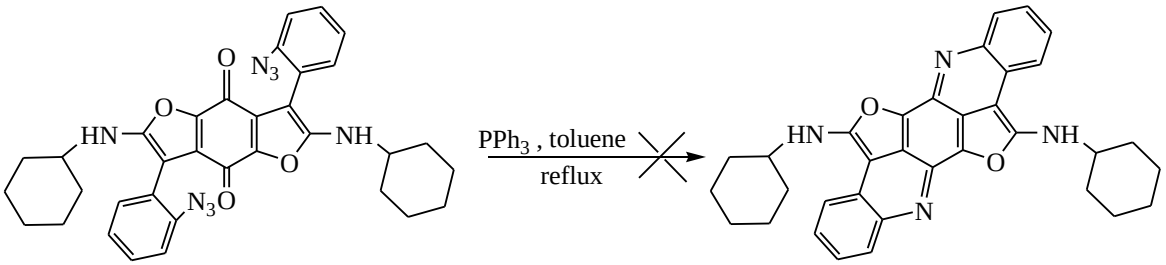
The reaction is thought to proceed through a condensation between 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione and 2-azidobenzaldehyde to produce the intermediate **485** which undergoes [1+4] cycloaddition with isocyanide to form intermediate **486**. Imine to enamine tautomerization of intermediate **486** produces compound **487** which, under the same reaction conditions, reacts again with 2-azidobenzaldehyde and cyclohexylisocyanide to form the ultimate product **483**, as shown in Scheme 2.122.




**481** **210** **484** **485** **486** **487** **483**

**Scheme 2.122**

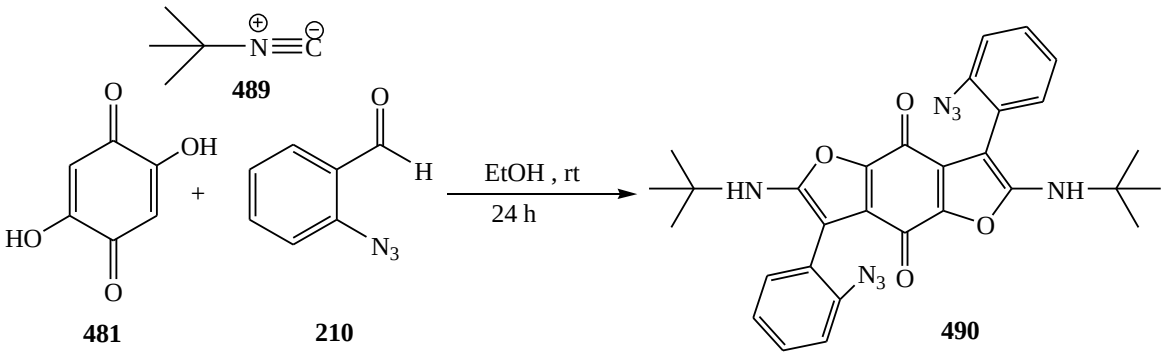
The reactivity of adduct **483** towards triphenylphosphine was investigated in an attempt to form cyclic imines **488** as a result of Staudinger-aza-Wittig reactions. Adduct **483** was unreactive to triphenylphosphine at room temperature as monitored by TLC. The reaction mixture was then heated at reflux to result only in the decomposition of the starting material. No products could be isolated and neither the imine **483** nor the iminophosphorane intermediate **488** were detectable.




**483** **488**

**Scheme 2.123**

The reaction of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione with 2-azidobenzaldehyde and tert-butyl isocyanide was also explored and also resulted in the synthesis of 2,6-bis (*tert*-butylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione **490** in 15 % yield (Scheme 2.124).




**489**

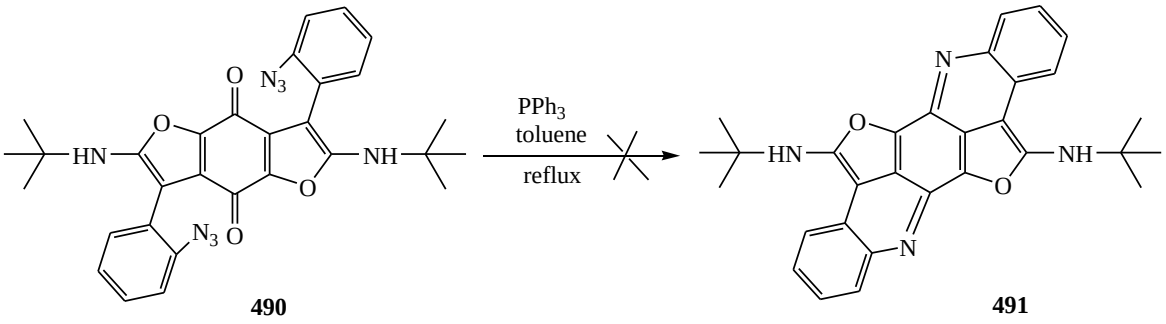
**481** **210** **490**

**Scheme 2.124**

The structure of the compound **490** was assigned tentatively and may not be correct because it is difficult to get full data[315] of compounds like **490**. The IR spectrum confirmed the presence of azide and carbonyl moieties with peaks at 2124 and 1737 $cm^{-1}$, respectively. $^{1}H$ NMR spectroscopy confirmed the presence of eighteen protons for six methyl groups as a

singlet at 1.32, and two protons of the NHs as a singlet at 6.29 ppm. $^{1}$H NMR spectroscopy also confirmed the presence of eight aromatic protons. $^{13}$C NMR spectroscopy further confirmed the structure by showing peaks at 28.19, 28.67 and 29.61 ppm for the methyl groups, whereas the presence of seven quaternary carbons and four CH peaks in the aromatic region confirmed the presence of the two aromatic rings and the symmetric tricyclic structure of the quinine **490**, although the $^{13}$C spectrum was complicated by lack of solubility and NMR invisibility seen in quinones.

The attempted reaction of adduct **490** with triphenylphosphine, like that with the cyclohexyl analogue **483**, was unsuccessful and no iminophosphorane or imine **491** was formed. Again, the compound **490** was found to be unstable in toluene at reflux.

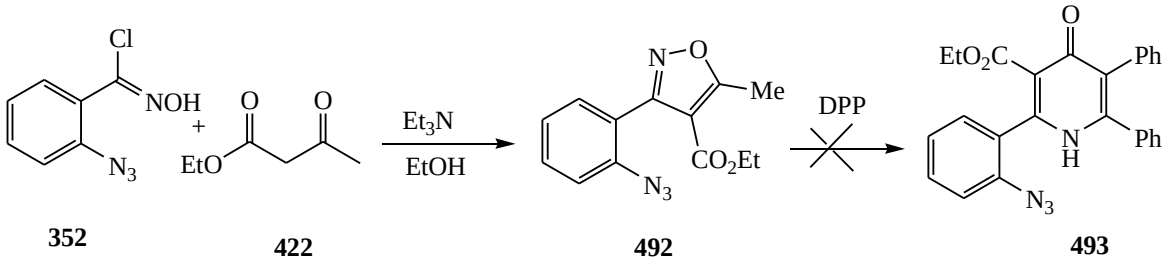



**490** **491**

**Scheme 2.125**

### 2.6.11. Synthesis of ethyl 3-(2-azidophenyl)-5-methylisoxazole-4-carboxylate.

The reaction of ethylacetoacetate with the nitrile oxide derived from 2-azidobenzohydroximoyl chloride **352** in the presence of triethylamine afforded the isoxazole **492** (Scheme 2.126) as a yellow oil. The isoxazole **492** is known in the literature[316] and was synthesized here because it might undergo reaction with DPP to produce the potential aza-Wittig precursor **493**. We hoped that this process might pave the way for a new MCR using 2-azidobenzohydroximoyl chloride **352**, active $CH_2$ compounds and cyclopropenones.

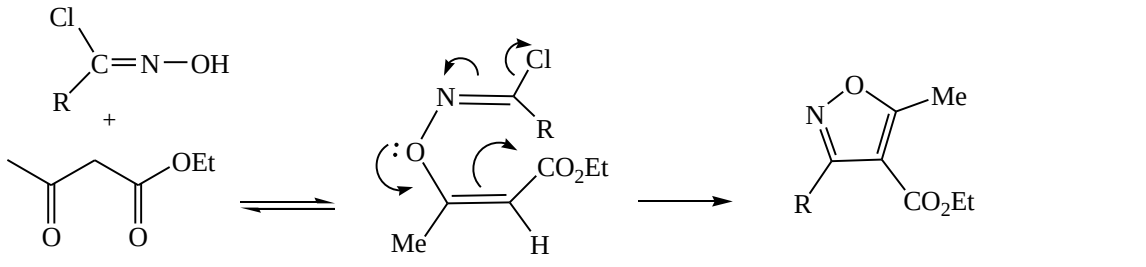



**352** **422** **492** **493**

**Scheme 2.126**

The structure of the initial product **492** was deduced from its IR, NMR and mass spectrometric data and was also identical to that produced in the literature. The IR spectrum confirmed the presence of azide and carbonyl moieties with peaks at 2123 and 1717 $cm^{-1}$. The $^{1}H$ NMR spectrum showed a triplet at 1.03 and a quartet at 4.08 ppm with a coupling constant of 5.8 Hz confirming the ethyl ester. One singlet at 2.64 ppm showed three protons of COMe and the rest of signals confirmed the four aromatic protons of the phenyl ring. The $^{13}C$ NMR spectrum confirmed the presence of a carbonyl group with a peak at 174.78 ppm. Three signals at 161.56, 159.70 and 109.77 ppm showed the three quaternary carbons of the isoxazole ring, whereas one peak at 13.07 ppm was consistent with the methyl substituent of the isoxazole ring. All other signals in the $^{13}C$ NMR spectrum and mass spectrometric data confirmed the structure of the product. The regiochemistry of the product was confirmed with HMBC and HSQC spectroscopic techniques, and by mechanistic analysis.

In the proposed mechanism, the reaction of triethylamine with ethyl acetoacetate formed an enolate intermediate which underwent stepwise nucleophilic addition with the nitrile oxide followed by elimination of water to produce the isoxazole.

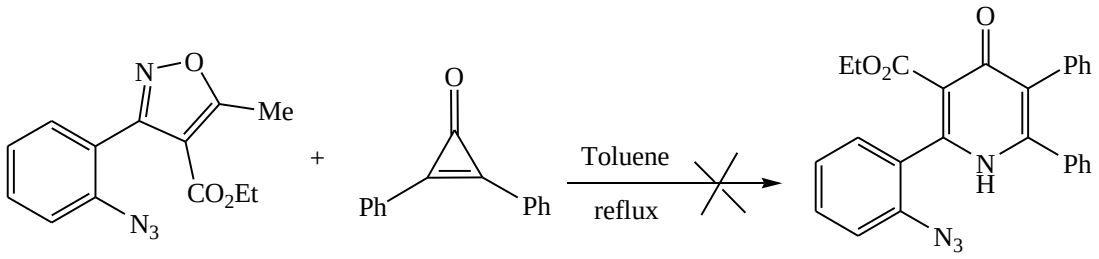



**422** **494** **492** R = 2-azidobenzyl

**Scheme 2.127**

The reactivity of adduct **492** was investigated by reacting it with diphenylcyclopropenone. It was envisaged that it would undergo Grigg's reaction[317] to form a pyridinone from the

isoxazole (as occurred with benzaldehyde) and that the presence of azide and carbonyl moieties in the anticipated product might lead to further reaction possibilities via a Staudinger-aza-Wittig reaction.




**492** **300** **493**

**Scheme 2.128**

The reaction mixture was heated in toluene at reflux for 24 hours and the only significant product identified was the dimer of diphenylcyclopropenone and the desired pyridone compound could not be found. This brief investigation based on the chemistry in Scheme 2.126 finished here.

## 2.7. Conclusion and future prospects.

A wide range of cyclic imines have been synthesized and their reactivity was examined against cyclopropenones and 1, 3-dipoles. Simple monocyclic 7-, 6- and 5-membered cyclic imines were reacted with different cyclopropenones to form examples of pyrroloazepine, indolizidine and pyrrolizidine products respectively. These bicyclic adducts were found to be stable in toluene at reflux and were unreactive towards dimethyl acetylenedicarboxylate. These reactions are currently being investigated in order to access pyrroloazepine, indolizidine and pyrrolizidine natural products.

4-Membered cyclic imines (1-azetines) were synthesized and reacted with different cyclopropenones to make azabicyclo compounds and the reactivity of these azabicyclic adducts was explored. A new protocol for the synthesis of pyridines was thus developed using the reaction of cyclopropenones with 4-aryl-1-azetines, which forms

azabicyclo[3.2.0]hept-2-ene-4-ones. When heated in toluene, the resulting azabicyclo[3.2.0]hept-2-en-4-ones generated the proposed 3-azacyclopentadienones which underwent Diels-Alder reaction with styrenes followed by extrusion of carbon monoxide to generate pyridines. The potential of the proposed 3-azacyclopentadienones was investigated in preliminary fashion in this programme of work and is currently being investigated further.

1,3-Dipolar cycloaddition of nitrile oxides to 4-aryl-2-alkylthio-1-azetines produced oxadiazabicyclo[3.2.0]heptenes that underwent formal [2+2] cycloreversion and loss of styrene to furnish stable 5-alkylthio-3-aryl-1,2,4-oxadiazoles in a similar process. In these reactions, a 2-alkylthio-1-azetine functions as a thiocyanate (R-S-CN) equivalent. The use of these oxadiazoles in Liebeskind style[318] coupling processes is under current investigation. 1,3-Dipolar cycloaddition of 2-azidobenzyl nitrile oxide to 2-methylthio-3,3,4,4-tetramethyl-1-azetine gave a oxadiazabicyclo[3.2.0]heptene that reacted with DMAD to unexpectedly produce a pyrimidine. This reaction should be more thoroughly investigated in future.

2-Methyl-3-phenyl-1-azirine, a 3-membered cyclic imine, was synthesized and reacted with diphenylcyclopropenone to furnish a mixture of pyridone and a pyrazine, a process that appeared to be catalysed by the diphenylcyclopropenone. This process warrants further investigation.

Some benzodiazepines and pyrrolobenzodiazepines were synthesized and converted into a range of benzodiazepine based cyclic imines. These cyclic imines were treated with cyclopropenones and nitrile oxides and were found to be unreactive towards both.
Due to this disappointment, 2-azidobenzaldehyde was synthesized and reacted in different multicomponent reactions to furnish a range of heterocyclic products that had azide, nitrile and/or carbonyl groups that might then undergo cycloaddition or aza-Wittig reaction. Staudinger-aza-Wittig reaction of diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate produced an imine and azide nitrile intramolecular cyclization in 2-(2-azidophenyl)-4-oxochroman-3-carbonitrile furnished a tetrazole ring. Several tetrazoles have been produced and this aspect of the MCRs reported in this thesis is under active development.

# *Chapter 3;*

# *Experimental*

# General information

Unless otherwise stated or unnecessary, all reactions were conducted under nitrogen dried through 4Å molecular sieves and delivered through a gas manifold using oven dried glass-ware. Work-up procedures were carried out in air. All solvents were purchased from Fisher Chemicals and were of analytical grade.

Anhydrous grade solvents were freshly distilled using a continuous still under nitrogen. Diethyl ether and THF were pre-dried over sodium wires, and then distilled over sodium wires (1-2 % w/v) and benzophenone (0.2-0.3 % w/v) as an indicator. Dichloromethane and toluene were dried over calcium hydride (5 % w/v) for 4-6 hours. Any other anhydrous solvents were purchased from Acros or Sigma-Aldrich, while deuterated solvents were purchased from Goss scientific.

All reactions were monitored by TLC, which was carried out on 0.20 mm Macherey-Nagel Alugram® Sil G/$UV_{254}$ silica gel-60 $F_{254}$ precoated aluminium plates and visulisation was achieved using UV light and / or using vanillin stain. Column chromatography was conducted using Merck silica gel (0.063-0.200 mm, 60 Å).

The NMR spectra were obtained on a Bruker DPX-400 or on a Bruker Avance 500 instrument. IR spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils and neat for solids. Mass spectra were recorded on a Bruker Daltonics micrOTOF mass spectrometer operating at a positive ion mode under an electrospray ionisation (ESI +) method. High resolution mass spectra were also recorded on a Finnegan MAT 900 XTL instrument operated by EPSRC National Mass Spectrometry service at the University of Swansea.

Melting points were measured by using a GallenKamp instrument.

Crystallographic data were recorded on a Bruker Apex Duo instrument at the University of Huddersfield.

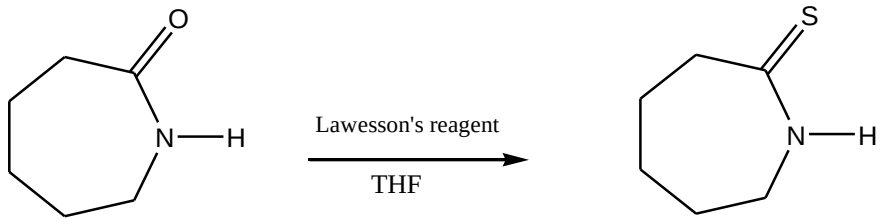
# 3. Experimental

## 3.1 Synthesis and reactivity of pyrroloazepines, indolizidines and pyrrolizidines.

### 3.1.1 Synthesis of pyrroloazepines, indolizidines and pyrrolizidines.

### 3.1.1.1 Synthesis of pyrroloazepines.

#### 3.1.1.1.1 Synthesis of azepan-2-thione.




**235** **236**

**Scheme 3.1**

To azepan-2-one (1 g, 8.85 mmol) in dry THF (15 ml) was added Lawesson's reagent (1.78 g, 4.42 mmol, 1.5 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 °C for 1h. The solvent was removed *in vacuo* to yield the crude product as an orange oil. It was purified by column chromatography (hexane / EtOAc : 4/1, Rf = 0.27) to yield as a white solid (1.08 g, 95 %) the azepan-2-thione, m.p. 117-120 °C.

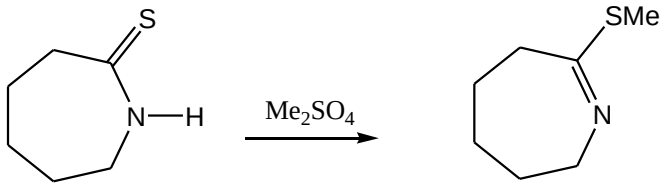
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3180 (m), 2928 (s), 1552 (s), 1439 (s), 1368 (m).

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.19 (1H, s, N*H*), 3.37 (2H, dd, *J*= 6.0, 10.1, $NCH_2$), 2.97 (2H, t, *J*= 5.4, $SCCH_2$) 1.79 – 1.73 (2H, m, $CH_2$), 1.72 – 1.66 (2H, m, $CH_2$), 1.64 – 1.58 (2H, m, $CH_2$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 210.31 (C=S), 47.25 ($CH_2$), 45.16 ($CH_2$), 30.52 ($CH_2$), 28.23 ($CH_2$), 24.62 ($CH_2$).

Data is identical to literature [229].

### 3.1.1.1.2. Synthesis of 2-methylthio-1-azepane

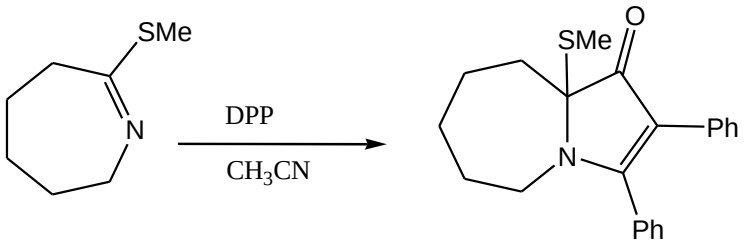



**236** **248**

**Scheme 3.2**

Dimethyl sulfate (0.485 ml, 5.11 mmol, 1.5 eq) was added in one portion to azepan-2-thione (440 mg, 3.41 mmol, 1 eq) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with diethyl ether (10 ml), washed with 10 % aqueous potassium carbonate (20 ml) and extracted with dichloromethane (3 x 20 ml). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave 2 ml of crude liquid which was used in the next step. (Note that 2-methylthio-1-azepane was found to be volatile and unstable)[319,320].

### 3.1.1.1.3 Synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[5.3.0]dec-2-en-4-one




**248** **249**

**Scheme 3.3**

Diphenylcyclopropenone (358 mg, 1.73 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-azepane (250 mg, 1.73 mmol, 1eq) dissolved in anhydrous acetonitrile (10 ml) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for 72 hours, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 4:1) to yield 5-methylthio-2,3-diphenyl-1-azabicyclo[5.3.0]dec-2-en-4-one (357 mg, 59 %) as a yellow oil.

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3053 (w) 2920 (m), 2851 (m), 1656 (vs), 1599 (s), 1577 (w), 1540 (s).

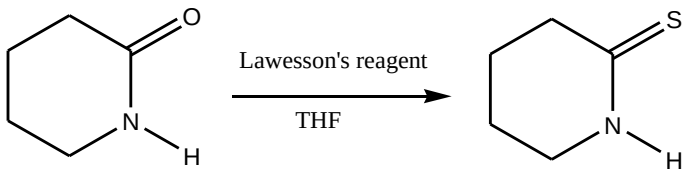
**$^{1}$H NMR δ (500 MHz, $CDCl_3$):** 7.53 – 7.46 (3H, m, Ar), 7.37 – 7.31 (2H, m, Ar), 7.13 – 7.10 (4H, m, Ar), 7.04 – 6.98 (1H, m, Ar), 3.82 – 3.78 (1H, m, NC$H_2$), 3.41 – 3.34 (1H, m, NC$H_2$), 2.78 (1H, dd, *J*= 7.8, 14.4, $CH_2$CSMe), 1.93 (3H, s, SMe), 1.77 – 1.64 (2H, m, $CH_2$), 1.71 (1H, dd, *J*= 11.4, 14.4, C$H_2$CSMe), 1.52 – 1.45 (1H, dd, *J*= 1.7, 14.1, $CH_2$), 1.31 – 1.21 (1H, m, $CH_2$), 1.18 – 1.10 (1H, m, $CH_2$), 1.10 – 1.01 (1H, m, $CH_2$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$):** 197.63 (C=O), 174.29 (q), 131.71 (q), 130.90 (q), 130.51 (CH), 129.37 (CH), 128.81 (CH), 128.51 (CH), 128.03 (CH), 125.66 (CH), 113.21 (q), 76.98 (q), 43.32 ($CH_2$), 37.27 ($CH_2$), 29.71 ($CH_2$), 29.53 ($CH_2$), 23.95 ($CH_2$), 11.56 ($CH_3$).

**HRMS (ESI+):** Found 372.1394 $[M+Na]^+$, $C_{22}H_{23}NNaOS$ requires 372.1392.

## 3.1.1.2 Synthesis of Indolizidines

### 3.1.1.2.1 Synthesis of piperidone-2-thione




**244** **245**

**Scheme 3.4**

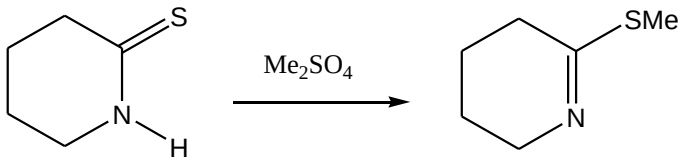
A solution of 2-piperidone (1 g, 10.58 mmol, 1 eq) and Lawesson's reagent (2.22 g, 5.49 mmol, 0.5 eq.) in anhydrous tetrahydrofuran (15 ml) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to reach ambient temperature, concentrated and purified by column chromatography (eluent: hexane: EtOAc 3:1, Rf = 0.24) to yield piperidine-2-thione (532 mg, 84 %) as white crystals, m.p. 114-117 $^{o}$C.

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.53 (1H, s, NH), 3.32 – 3.28 (2H, m, NC*H*$_2$), 2.82 (2H, t, *J*= 6.3 Hz, $SCCH_2$), 1.78 – 1.67 (4H, m, $CH_2CH_2CH_2CH_2$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 202.11 (C=S), 44.60 ($CH_2$), 39.11 ($CH_2$), 20.70 ($CH_2$), 20.09 ($CH_2$).

The data is identical to literature [229].

### 3.1.1.2.2 Synthesis of 2-methylthio-1-piperidine

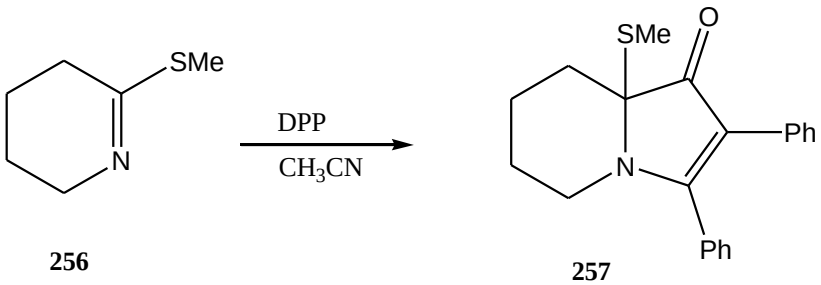



**245** **256**

**Scheme 3.5**

Dimethyl sulfate (611 mg, 0.46 mL, 4.78 mmol, 1.1 eq.) was added in one portion to piperidine-2-thione (500 mg, 4.34 mmol, 1 eq) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 ml), washed with 10 % potassium carbonate (20 ml) and extracted with dichloromethane (3 x 20 ml). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave 2 ml of liquid which was used crude in the next step. (Note that 2-methylthio-1-piperidine was found to be volatile and unstable)[319,320].

### 3.1.1.2.3 Synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one




**256** **257**

**Scheme 3.6**

Diphenylcyclopropenone (475 mg, 2.30 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-piperidine (300 mg, 2.30 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 ml) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for a week, concentrated and purified by column chromatography (eluent: hexane:EtOAc, 4:1, Rf = 0.32) to yield 5-methylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one (427 mg, 55 %) as an orange/ yellow oil.

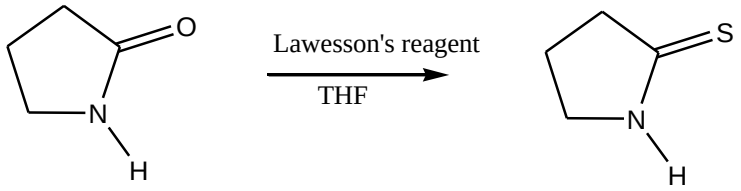
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3056 (w), 2941 (m), 2859 (w), 1655 (vs), 1599 (m), 1578 (w), 1537 (m).

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 7.52 – 7.45 (3H, m, Ar), 7.34 – 7.28 (2H, m, Ar), 7.15 – 7.09 (4H, m, Ar), 7.05 – 7.00 (1H, m, Ar). 3.65 (1H, dd, *J*= 8.7 and 4.7 Hz, $NCH_2$), 3.51 (1H, td, *J*= 3.2 and 9.8 Hz $NCH_2$), 2.28 – 2.21 (1H, m, $SCCH_2$), 1.98 (3H, s, $SCH_3$), 1.97 – 1.74 (3H, m), 1.73 – 1.65 (1H, m), 1.36 – 1.29 (1H, m).
**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 198.75 (C=O), 170.55 (q), 131.65 (q), 130.34 (q), 130.30 (CH), 129.17 (CH), 128.48 (CH), 128.19 (CH), 127.78 (CH), 125.23 (CH), 109.86 (q), 72.19 (q), 41.40 ($CH_2$), 32.62, ($CH_2$), 27.37 ($CH_2$), 20.45 ($CH_2$), 10.56 ($CH_3$).

**HRMS (ESI+):** Found 358.1234 $[M+H]^+$, $C_{20}H_{19}NO_2$ requires 358.1236.

## 3.1.1.3 Synthesis of pyrrolizidines.

### 3.1.1.3.1 Synthesis of pyrrolidine-2-thione




**246** **247**

**Scheme 3.7**

A solution of pyrrolidine-2-one (1 g, 11.75 mmol, 1 eq) and Lawesson's reagent (2.37 g, 5.87 mmol, 0.5 eq.) in anhydrous tetrahydrofuran (15 ml) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to reach ambient temperature, concentrated and purified by column chromatography (eluent: hexane: EtOAc 3:1, Rf = 0.23) to yield pyrrolidine-2-thione (532 mg, 90 %) as white crystals, m.p. 108-112 $^{o}$C.

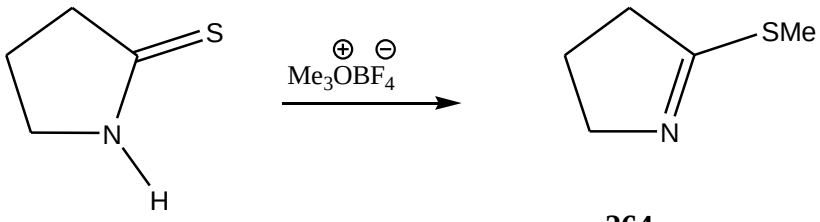
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3139 (br, **NH**), 2916 (w), 2884 (w), 1533 (m, **C=S**), 1469 (w), 1445 (m), 1291(s), 1214 (m).

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 8.74 (1H, s, NH), 3.63 (2H, t, *J*= 7.3 Hz, NC*H*$_2$), 2.92 (2H, t, *J*= 8.0 Hz, SC$CH_2$), 2.21 (2H, m, $CH_2CH_2CH_2$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 206.07 (C=S), 49.86 ($CH_2$), 43.21 ($CH_2$), 22.87 ($CH_2$).

The data is identical to literature [229].

### 3.1.1.3.2 Synthesis of 5-(methylthio)-3,4-dihydro-2*H*-pyrrole

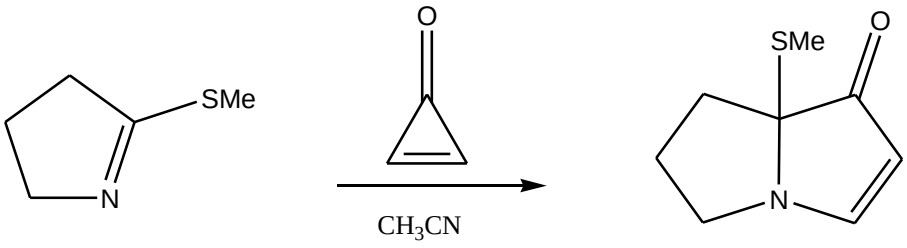



**247** **264**

**Scheme 3.8**

Meerwein's reagent (878 mg, 5.94 mmol, 1.2 eq.) was added in one portion to pyrrolidine-2-thione (500 mg, 4.95 mmol, 1 eq) in anhydrous DCM (10 ml) and the mixture was stirred for 1 hour at ambient temperature under an atmosphere of dry nitrogen and then heated at reflux for 1 hour. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C. The solution was then filtered through Celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration, the solvent was evaporated *in vacuo* to leave 2 ml of liquid product as dark orange oil which was used crude in the next step. (Note that 2-methylthio-1-piperidine was found to be volatile and unstable)[319].

### 3.1.1.3.3 Synthesis of 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one




**264** **265**

**Scheme 3.9**

Cyclopropenone (140 mg, 2.60 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-pyrrolidine (300 mg, 2.60 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 ml) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for 12 hours, concentrated and purified by column chromatography (eluent: hexane:EtOAc, 4:1, Rf = 0.36) to yield 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one (81 mg, 18 %) as a yellow oil.

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 2980 (br), 2851 (m), 1681 (s), 1597 (m), 1533 (m), 1341 (m).

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.77 (1H, d, *J*= 3.5 Hz, C=CH), 5.35 (1H, d, *J*= 3.6 Hz, C=CH), 3.49-3.56 (1H, m, NCH), 3.30-3.36 (1H, m, NCH), 2.05-2.22 (2H, m, $CH_2$), 1.96 (3H, s, $SCH_3$), 1.85-1.93 (2H, m, $CH_2$).

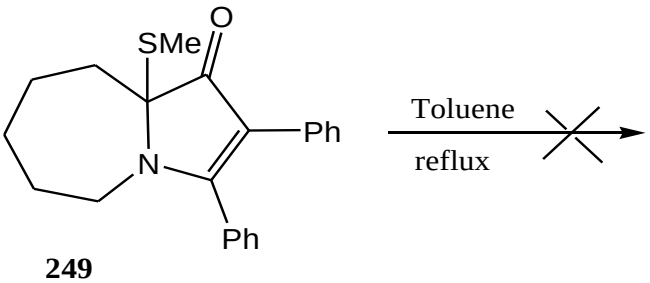
**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 203.54 (C=O), 169.00 (CH), 105.24 (CH), 79.46 (C), 48.46 ($CH_2$), 32.86 ($CH_2$), 27.07 ($CH_2$), 11.84 ($CH_3$).

**HRMS (ESI+):** Found 192.0454, $C_8H_{11}NOSNa$, requires 192.0454.

## 3.1.2 Reactivity of pyrroloazepines, indolizidines and pyrrolizidines

### 3.1.2.1 Reactivity of pyrroloazepines.

#### 3.1.2.1.1. Reactivity of 5-methylthio-2,3-diphenyl-1-azabicyclo[5.3.0]dec-2-en-4-one.



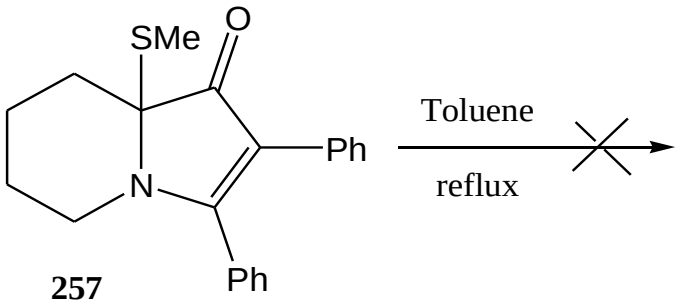

**249**

**Scheme 3.10**

100 mg (0.28 mmol) of 5-methylthio-2,3-diphenyl-1-azabicyclo[5.3.0]dec-2-en-4-one was added to toluene (10 ml) and the mixture was heated at 115 $^{o}$C overnight. The reaction was monitored by TLC and even after 72 hours of reflux no product could be identified.

## 3.1.2.2 Reactivity of indolizidines.

### 3.1.2.2.1. Reactivity of 5-methylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one.



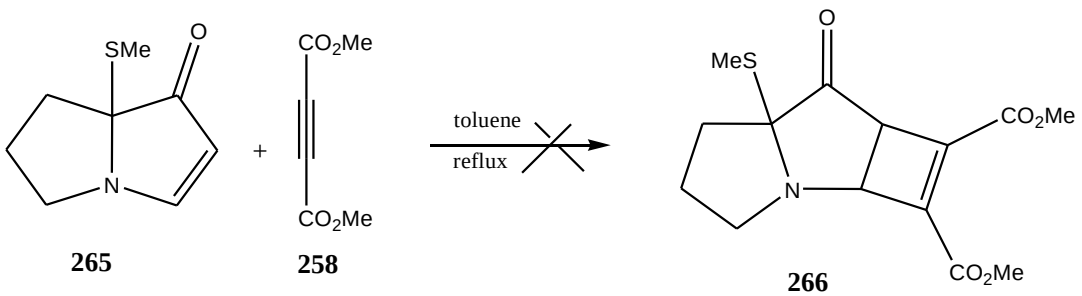

**257**

**Scheme 3.11**

100 mg (0.30 mmol) of 5-methylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one was added to toluene (10 ml) and the mixture was heated at 115 $^{o}$C overnight. The reaction was monitored by TLC and even after 72 hours of reflux no product could be identified.

## 3.1.2.3 Reactivity of pyrrolizidines.

### 3.1.2.3.1. Reactivity of 5-(methylthio)-1-azabicyclo[3.3.0]oct-2-en-4-one with DMAD




**265** **258** **266**

**Scheme 3.12**

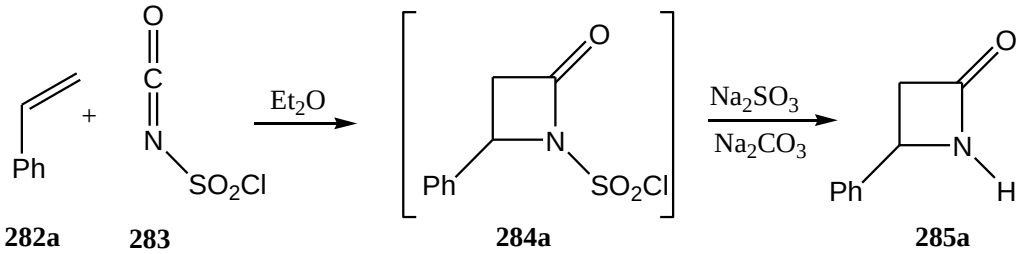
5-(methylthio)-1-azabicyclo[3.3.0]oct-2-en-4-one **(**70 mg, 0.41 mmol) and DMAD (58.8 mg, 0.3 ml, 1 eq.) were added to toluene (10 ml) and the mixture was heated at 115 $^{o}$C for 24 hours. The reaction was monitored by TLC and then mixture was refluxed for 12 hours and monitored again, no product could be identified.

## 3.2 Synthesis and reactivity of 1-azetines

### 3.2.1 Synthesis of 1-azetines

#### 3.2.1.1 Synthesis of 2-methylthio-4-phenyl-1-azetine

##### 3.2.1.1.1. Synthesis of 4-phenylazetidin-2-one




**282a** **283** **284a** **285a**

**Scheme 3.13**

N-chlorosulfonyl isocyanate (CSI) (3.20 ml, 5.24g, 37.0 mmol, 1.2 eq.) was added drop wise to styrene (3.7 ml, 3.32g, 31.90 mmol) in dry diethyl ether (15 ml) under an inert atmosphere over 10 minutes. The mixture was stirred at room temperature for 2h and the solvent was removed *in vacuo* to give an oily residue, which was redissolved in diethyl ether (20 ml) and added over 10 minutes to a vigorously stirred solution of water (30 ml), sodium carbonate (9 g, 107.1 mmol, 3.3 eq.), sodium sulfite (6 g, 47.6 mmol, 1.5 eq.) and ice (20 g). The solution was stirred for 1 hour and filtered under vacuum. The organic layer was separated, and the aqueous layer was washed with diethyl ether (5 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent evaporated under vacuum to yield the product as a white solid (3.70 g, 79 %, m.p. = 102-103 $^{o}$C) [247].

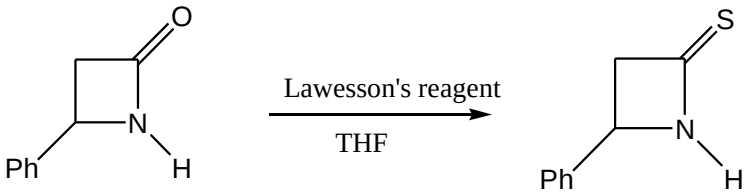
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3207 (br, NH), 1737 (m), 1705 (s, C=O), 1491 (m), 1453 (m), 1404 (m) 1390 (w), 1368 (m), 1282 (w), 1214 (w), 1185 (m), 1171 (m), 1007 (w), 979 (m), 962 (m), 783 (w), 757 (s), 697 (s).

**$^1$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.34-7.27 (5H, m, Ph), 6.97 (1H, bs, NH), 4.67 (1H, dd, *J*= 5.2 and 2.3 Hz, CH), 3.38 (1H, ddd, *J*= 14.8, 5.2 and 2.3 Hz, $CH_2$), 2.80 (1H, dd, *J*= 14.8 and 2.3 Hz, $CH_2$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 168.48 (C=O), 140.13 (C), 128.44 (CH), 127.93 (CH), 125.47 (CH), 50.15 (CH), 47.60 ($CH_2$).

**MS (m/z):** 170 $(M+Na)^+$, 317 $(2M+Na)^+$.

### 3.2.1.1.2 Synthesis of 4-phenylazetidin-2-thione




**285a** **286a**

**Scheme 3.14**

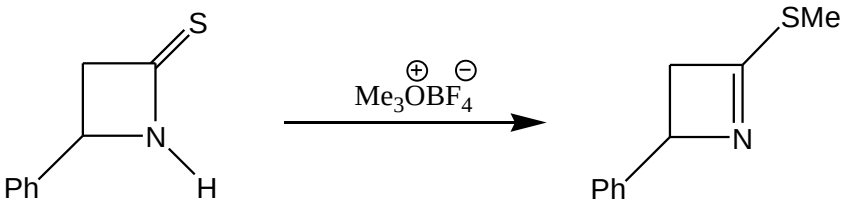
To 4-phenylazetidine-2-one (3.70 g, 25.17 mmol) in dry THF (15 ml) was added Lawesson's reagent (5.08 g, 12.58 mmol, 0.5 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^oC$ for 20 minutes. The solvent was then removed by rotary evaporation to yield the crude product as orange oil. It was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 3/1, Rf = 0.24) to yield a white solid (1.97g, 48 %, m.p. = 117-118 $^oC$) [247].

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3136 (br, NH), 1486 (s, C=S), 1450 (s), 1403 (m), 1359 (m), 1263 (w), 1236 (s) 1176 (m), 1146 (m), 1068 (w), 980 (m), 963 (s), 756 (s), 694 (s).

**$^1$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 8.28 (1H, bs, NH), 7.38-7.31 (5H, m, Ph), 5.18 (1H, dd, *J*= 4.6 and 1.8 Hz, CH), 3.51 (1H, ddd, *J*= 15.5, 4.6 and 2.1 Hz, $CH_2$), 3.02 (1H, dd, *J*= 15.5 and 1.8 Hz, $CH_2$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 204.42 (C=S), 138.03 (C), 129.03 (CH), 128.82 (CH), 125.77 (CH), 58.89 (CH), 51.26 ($CH_2$).

### 3.2.1.1.3 Synthesis of 2-methylthio-4-phenyl-1-azetine




**286a** **287a**

**Scheme 3.15**

To 4-phenylazetidin-2-thione (500 mg, 3.06 mmol) was added Meerwein's reagent (785 mg, 5.34 mmol, 1.5 eq.) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^oC$. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give the product as dark orange oil (237 mg, 43 %).

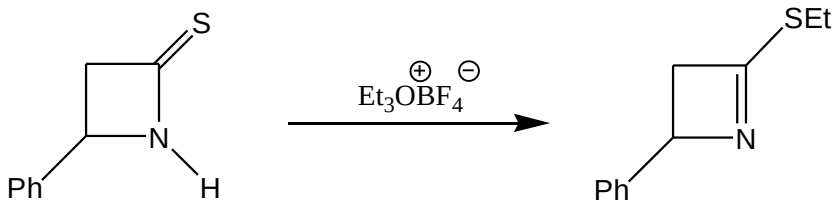
**IR: $\upsilon_{max}$ ($cm^{-1}$):** 2940 (w), 1523 (s), 1500 (m), 1460 (m), 1225 (s), 1135 (w), 960 (m), 920 (m).

**$^1$H NMR: δ (400 MHz, $CDCl_3$):** 7.34 – 7.29 (5H, m, 5 x PhH), 5.25 (1H, dd, *J* = 4.3, 1.9, CH), 3.56 (1H, dd, *J* = 14.5 and 4.3, $CH_2$), 2.95 (1H, dd, *J* = 14.5 and 1.9, $CH_2$), 2.48 (3H, s, Me).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 183.31 (C), 140.03(C), 127.48 (CH), 126.42 (CH), 125.37 (CH), 64.17 (CH), 42.50 ($CH_2$), 11.51 (Me).

**HRMS (m/z):** calc for $C_{10}H_{11}NS + H^+$ ($M + H^+$), 178.0687, found 178.0689

### 3.2.1.2 Synthesis of 2-ethylthio-4-phenyl-1-azetine




**286a** **287b**

**Scheme 3.16**

To 4-phenylazetidin-2-thione (500 mg, 3.06 mmol) was added Meerwein's reagent (1M solution in DCM, 5 ml, 5 mmol, 1.6 eq.) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give the product as dark orange oil (320 mg, 54 %).

**IR: $\upsilon_{max}$ ($cm^{-1}$):** 3059 (w), 3030 (w), 2968 (w), 2926 (w), 1655 (m), 1554 (m), 1514 (m), 1493, (m), 1450 (m), 1374 (m), 1325 (m), 1264 (m), 1029 (m), 972 (m), 755 (m), 697 (s).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.34-7.28 (5H, m, Ph), 5.02 (1H, dd, *J* = 4.3 and 2.0, CH), 3.56 (1H, dd, *J* = 14.6 and 4.3, $CH_2$), 3.06 (2H, q, *J* = 7.4, $SCH_2Me$), 2.96 (1H, dd, *J* = 14.6 and 2.0, $CH_2$), 1.40 (3H, t, *J* = 7.4, $SCH_2CH_3$).

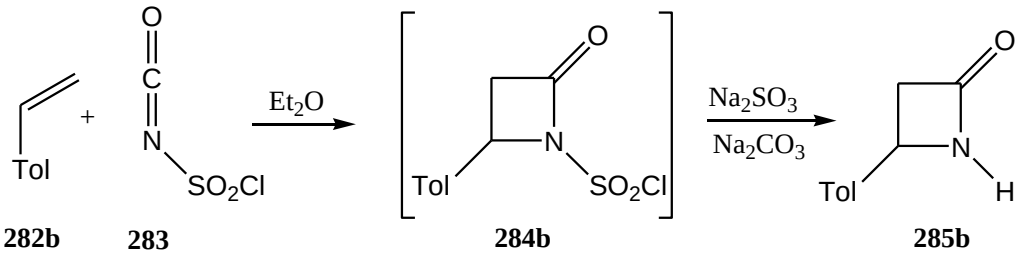
**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 183.56 (C), 140.82 (C), 128.37 (CH), 127.34 (CH), 125.96 (CH), 65.10 (CH), 43.57 ($CH_2$), 23.36 ($CH_2$), 14.65 ($CH_3$).

**MS (m/z):** 192.1 ($[M+H]^+$), 383.2 ($[M_2+H]^+$), 574.2 ($[M_3+H]^+$), 765.3 ($[M_4+H]^+$), 956.4 ($[M_5+H]^+$).

**HRMS (m/z):** calc for $C_{11}H_{13}NS + H^+$ ($M + H^+$), 192.0843, found 192.0845.

## 3.2.1.3 Synthesis of 2-methylthio-4-tolyl-1-azetine

### 3.2.1.3.1. Synthesis of 4-tolylazetidin-2-one




**282b** **283** **284b** **285b**

**Scheme 3.17**

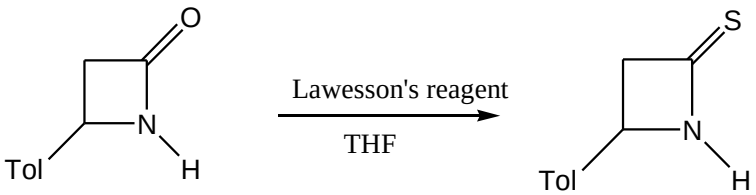
N-chlorosulfonyl isocyanate (CSI) (1.76 ml, 2.86 g, 20.30 mmol, 1.2 eq.) was added dropwise to vinyltoluene (2.2 ml, 2 g, 16.92 mmol) in dry diethyl ether (15 ml) under an inert atmosphere over 10 minutes. The mixture was stirred at room temperature for 2h and the solvent was removed *in vacuo* to give an oily residue, which was redissolved in diethyl ether (20 ml) and added over 10 minutes to a vigorously stirred solution of water (30 ml), sodium carbonate (4.5 g, 42.50 mmol, 2.5 eq.), sodium sulfite (3 g, 22.41 mmol, 1.3 eq.) and ice (20 g). The solution was stirred for 1 hour and filtered under vacuum. The organic layer was separated, and the aqueous layer was washed with diethyl ether (5 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent evaporated under vacuum to yield the product as a white solid (2.27 g, 83 %, m.p. = 104-107 $^{o}$C).

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3216 (br, NH), 1769.5 (s, C=O), 1513.4 (m), 1417 (m), 1375 (m), 1351 (w), 1275 (m), 1177 (w), 1114 (w), 966 (m), 814 (m), 774 (w), 623 (m), 556 (m), 486 (w), 408 (s).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.27 (2H, d, *J*= 8.1, Ph), 7.20 (2H, d, *J*= 8.3, Ph), 6.74 (1H, bs, NH), 4.69 (1H, dd, *J*= 5.2 and 2.4 Hz, CH), 3.42 (1H, ddd, *J*= 14.8, 5.2 and 2.4 Hz, $CH_2$), 2.84 (1H, dd, *J*= 14.8 and 2.0 Hz, $CH_2$), 2.37 (3H, $CH_3$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 168.63 (C=O), 137.99 (C)), 137.25 (CH), 129.35 (CH), 125.91 (CH), 50.37 (CH), 47.93 ($CH_2$), 21.19 ($CH_3$).

### 3.2.1.3.2. Synthesis of 4-tolylazetidin-2-thione




**285b** **286b**

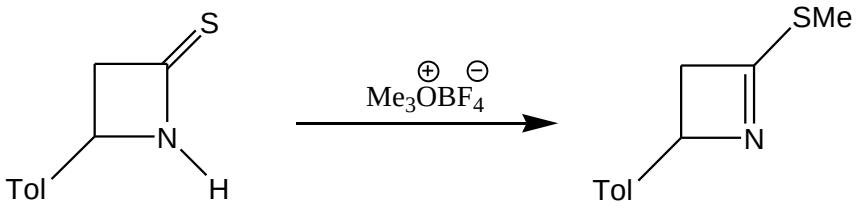
**Scheme 3.18**

To 4-tolylazetidine-2-one (1.1 g, 6.79 mmol) in dry THF (15 ml) was added Lawesson's reagent (1.37 g, 3.39 mmol, 0.5 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^{o}$C for 20 minutes. The solvent was then removed by rotary evaporation to yield the crude product as an orange oil. It was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 3/1, Rf = 0.24) to yield a white solid ( 0.58 g, 52 %, m.p. = 114-117 $^{o}$C).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 8.84 (1H, bs, NH), 7.33-7.26 (4H, m, Ph), 5.15 (1H, dd, *J*= 4.5 and 1.8 Hz, CH), 3.48 (1H, ddd, *J*= 15.5, 4.5 and 2.0 Hz, $CH_2$), 3.97 (1H, dd, *J*= 15.6 and 1.5 Hz, $CH_2$), 2.37 (3H, $CH_3$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 204.48 (C=S), 138.71 (C), 135.05 (CH), 129.69 (CH), 125.64 (CH), 58.97 (CH), 51.23 ($CH_2$), 21.25 ($CH_3$).

### 3.2.1.3.3. Synthesis of *2-methylthio-4-tolyl-1-azetine*




**286b** **287c**

**Scheme 3.19**

To 4-tolylazetidin-2-thione (500 mg, 3.56 mmol) was added Meerwein's reagent (785 mg, 5.34 mmol, 1.5 eq.) in dry dichloromethane (15 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C and filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give the product as dark orange oil (220 mg, 41 %).

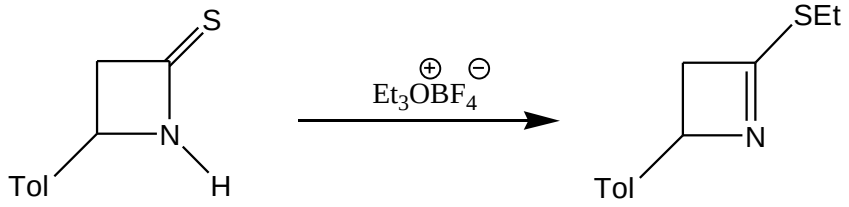
**IR $\upsilon_{max}$ ($cm^{-1}$):** 2935 (w), 1523 (s), 1400 (w), 1224 (s), 1135 (m), 941 (m), 905 (m), 811 (s).

**$^{1}$H NMR: δ (400 MHz, $CDCl_3$):** 7.27 (2H, d, *J* = 8.0, 2 x ArH), 7.19 (2H, d, *J* = 8.0, 2 x ArH), 5.01 (1H, dd, *J* = 4.3, 2.0, CH), 3.56 (1H, dd, *J* = 14.6 and 4.3, $CH_2$), 2.96 (1H, dd, *J* = 14.6 and 2.0, $CH_2$), 2.49 (3H, s, Me), 2.37 (3H, s, Me).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 183.12 (C), 137.10 (C), 136.44 (C), 128.47 (CH), 125.57 (CH), 64.14 (CH), 42.38 ($CH_2$), 20.53 (Me), 10.85 (Me).

**HRMS (m/z):** calc for $C_{11}H_{13}NS + H^+$ (M + $H^+$), 192.0843, found 192.0843.

### 3.2.1.4. Synthesis of *2-ethylthio-4-tolyl-1-azetine*




**286b** **287d**

**Scheme 3.20**

To 4-tolylazetidin-2-thione (500 mg, 2.80 mmol) was added Meerwein's reagent (1 M solution in DCM, 4.21 ml, 4.21 mmol, 1.5 eq.) in dry dichloromethane (10 ml) under a

nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give the product as dark orange oil (221 mg, 38 %).

**IR $\upsilon_{max}$ (cm$^{-1}$):** 3251 (w), 1522 (s), 1440 (w), 1224 (s), 1134 (m), 940 (m), 911 (m), 811 (s).

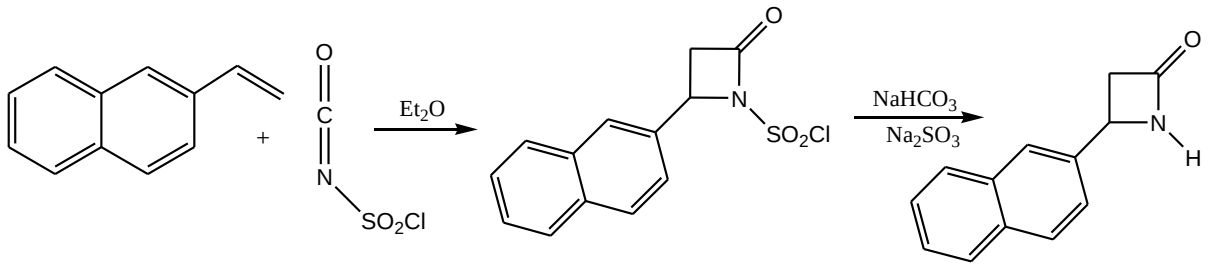
**$^{1}$HNMR: δ (400 MHz, $CDCl_3$):** 7.13 (2H, d, *J* = 8.0, 2 x ArH), 7.04 (2H, d, *J* = 8.0, 2 x ArH), 4.88 (1H, dd, *J* = 4.2, 1.9, CH), 3.47 (1H, dd, *J* = 14.5 and 4.2, $CH_2$), 2.98 (2H, dq, *J* = 7.2 and 1.8, $SCH_2$), 2.86 (1H, dd, *J* = 14.5 and 1.9), 2.27 (3H, s, Me), 1.33 (3H, t, *J* = 7.2, $SCH_2CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 183.10 (C), 137.11 (C), 136.65 (C), 128.11 (CH), 124.07 (CH), 64.97 (CH), 44.31 ($CH_2$), 22.50 (Me), 20.10 ($CH_2$), 13.43 (Me).

**HRMS (m/z):** calc for $C_{12}H_{15}NS + H^+$ (M + $H^+$), 206.0999, found 206.1002.

## 3.2.1.5 Synthesis of *2-methylthio-4-naphthyl-1-azetine*

### 3.2.1.5.1. Synthesis of 4-naphthylazetidin-2-one




**282c** **283** **284c** **285c**

**Scheme 3.21**

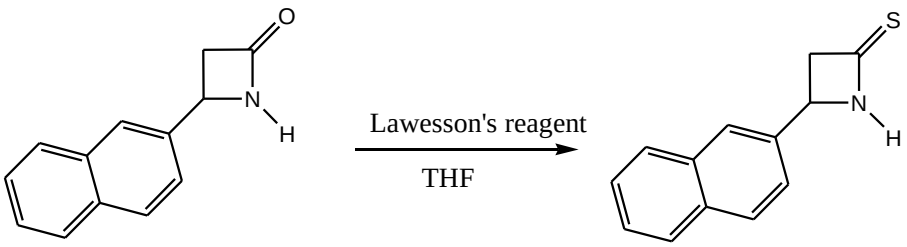
N-chlorosulfonyl isocyanate (CSI) (1.35 ml, 2.20 g, 15.55 mmol, 1.2 eq.) was added dropwise to 2-vinylnaphthalene (2 g, 12.96 mmol) in dry diethyl ether (15 ml) under an inert atmosphere over 10 minutes. The mixture was stirred at room temperature for 2h and the solvent was removed *in vacuo* to give an oily residue, which was redissolved in diethyl ether (20 ml) and added over 10 minutes to a vigorously stirred solution of water (30 ml), sodium carbonate (4.5 g, 42.50 mmol), sodium sulfite (3 g, 22.38 mmol) and ice (20 g). The solution was stirred for 1 hour and filtered under vacuum. The organic layer was separated, and the aqueous layer was washed with diethyl ether (5 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent evaporated under vacuum to yield the product as a white solid (1.64 g, 64 %, m.p. = 105-108 $^{o}$C).

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3152 (br, NH), 1709 (s, C=O), 1402 (s), 1266 (m), 1233 (s) 1168 (m), 1123 (m), 941 (m), 926 (s), 866 (s), 822 (s).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.90-7.81 (5H, m, Ar), 7.48 (2H, dd, *J*= 8.4 and 1.7 Hz, Ar), 6.69 (1H, bs, NH), 4.85 (1H, dd, *J*= 4.9 and 2.1 Hz, CH), 3.52 (1H, ddd, *J*= 15.6, 5.6 and 2.2 Hz, $CH_2$), 2.84 (1H, dd, *J*= 14.8 and 1.8 Hz, $CH_2$), 2.37 (3H, $CH_3$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 168.4 (C=O), 137.5 (C (Ar)), 134.0 (C (Ar)), 129.1 (C (Ar)), 128.5 (C (Ar), 128.1 (C (Ar), 127.8 (C (Ar), 127.1 (C (Ar), 126.3 (C (Ar)), 124.7 (C (Ar), 50.58 (CH), 47.90 ($CH_2$).

### 3.2.1.5.2. Synthesis of *4-naphthylazetidin-2-thione*




**285c** **286c**

**Scheme 3.22**

To 4-naphthylazetidine-2-one (750 mg, 3.81 mmol) in dry THF (15 ml) was added Lawesson's reagent (770 mg, 1.90 mmol, 0.5 eq.) under an inert atmosphere and the mixture

was stirred at room temperature for 1 h and then at 60 $^{o}$C for 20 minutes. The solvent was then removed by rotary evaporation to yield the crude product as orange oil. It was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 3/1, Rf = 0.24) to yield a white solid (378 mg, 47 %, m.p. = 119-122 $^{o}$C).

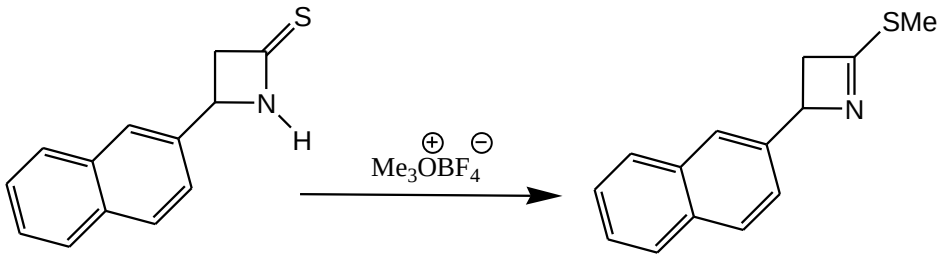
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3132 (br, NH), 1499 (s, C=S), 1402 (s), 1263 (m), 1237 (s) 1168 (m), 1121 (m), 941 (m), 916 (s), 866 (s), 820 (s).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.91-7.81 (3H, m, Ar), 7.54 (m, 2H, Ar), 7.48 (2H, dd, *J*= 8.4 and 1.7 Hz, Ar), 7.3 (1H, bs, NH), 5.4 (1H, dd, *J*= 4.9 and 2.1 Hz, CH), 3.52 (1H, ddd, *J*= 15.6, 5.6 and 2.2 Hz, $CH_2$), 3.12 (1H, dd, *J*= 14.4 and 1.9 Hz, $CH_2$).

**$^{13}$C NMR $\delta_c$ (125 MHz, $CDCl_3$)** 204.4 (C=O), 135.4 (C (Ar)), 133.3 (C (Ar)), 133.1 (C (Ar)), 129.2 (C (Ar), 128.1 (C (Ar), 127.8 (C (Ar), 126.6 (C (Ar), 122.9 (C (Ar)), 59.12 (CH), 51.25 ($CH_2$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.1.5.3. Synthesis of *2-methylthio-4-naphthyl-1-azetine*




**286c** **287 e**

**Scheme 3.23**

To 4-naphthylazetidin-2-thione (300 mg, 1.40 mmol) was added Meerwein's reagent (312 mg, 2.11 mmol, 1.5 eq.) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C.

The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the product as a dark orange oil (133 mg, 40 %).

**IR $\upsilon_{max}$ ($cm^{-1}$):** 3023 (w), 2915 (w), 1604 (m), 1510 (w), 1490 (m), 1345 (m), 1165 (s), 1072 (s), 819 (s), 749 (s).

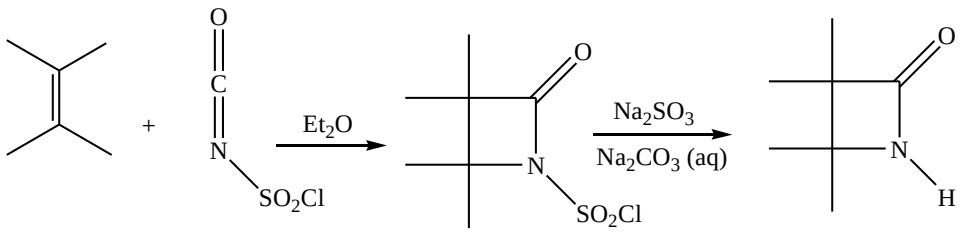
**$^1$H NMR: δ (400 MHz, $CDCl_3$):** 7.76 – 7.69 (4H, m, 4 x ArH), 7.31 – 7.39 (3H, m, 3 x ArH), 5.07 (1H, dd, *J* = 4.3, 2.0, CH), 3.51 (1H, dd, *J* = 14.6 and 4.3, $CH_2$), 2.94 (1H, dd, *J* = 14.6 and 2.0), 2.41 (3H, s, Me).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 183.35 (C), 136.95 (C), 133.37 (C), 132.66 (C), 128.10 (CH), 127.59 (CH). 127.44 (CH), 126.64 (CH), 126.25 (CH), 124.40 (CH), 123.17 (CH), 64.87 (CH), 43.45 ($CH_2$), 11.11 (SMe).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

## 3.2.1.6. Synthesis of 2-methylthio-3,3,4,4-tetramethyl-1-azetine

### 3.2.1.6.1. Synthesis of 3,3,4,4-tetramethylazetidin-2-one




**294** **283** **295** **296**

**Scheme 3.24**

N-chlorosulfonyl isocyanate (CSI) (1.75 ml, 2.83 g, 20 mmol, 1.2 eq.) was added dropwise to 2,3-dimethyl-2-butene (1.4 g, 2 ml, 16.66 mmol) in dry diethyl ether (15 ml) under an inert atmosphere over 10 minutes. The mixture was stirred at room temperature for 2h and the

solvent was removed *in vacuo* to give an oily residue, which was redissolved in diethyl ether (20 ml) and added over 10 minutes to a vigorously stirred solution of water (30 ml), sodium carbonate (4.5 g, 42.5 mmol), sodium sulfite (3 g, 22.38 mmol) and ice (20 g). The solution was stirred for 1 hour and filtered under vacuum. The organic layer was separated, and the aqueous layer was washed with diethyl ether (5 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent evaporated under vacuum to yield the product as a white solid (1.51 g, 71 %, m.p. = 102-104 $^{o}$C) [247].

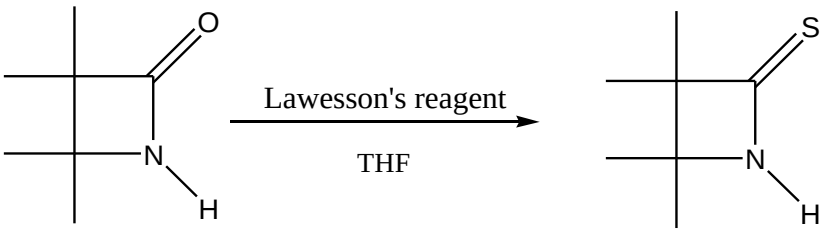
**IR $\upsilon_{max}$ (cm$^{-1}$):** 3186 (br, NH), 2984 (w), 1747 (m), 1703 (s, C=O), 1449 (w), 1393 (m), 1375 (m), 1314 (m), 1252 (w).

**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 6.02 (1H, bs, NH), 1.32 (6H, s, 2 x $CH_3$), 1.22 (6H, s, 2 x $CH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 174.91 (C=O), 58.18 (C), 54.51 (C), 24.40 ($CH_3$), 19.06 ($CH_3$).

**MS (m/z) :** 150.1 $[M+Na]^+$, 255.2 $[M_2+H]^+$, 277.2 $[M_2+Na]^+$.

### 3.2.1.6.2. Synthesis of 3,3,4,4-tetramethylazetidin-2-thione




**296** **297**

**Scheme 3.25**

To 3,3,4,4-tetramethylazetidine-2-one (1 g, 7.87 mmol) in dry THF (15 ml) was added Lawesson's reagent (1.59 g, 3.93 mmol, 0.5 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^{o}$C for 20 minutes. The solvent was then removed by rotary evaporation to yield the crude product as orange oil. It was purified

by column chromatography (PE 40-60 $^{o}$C / EtOAc : 3/1, Rf = 0.24) to yield a white solid (521 mg, 47 %, m.p. = 121-124 $^{o}$C) [247].

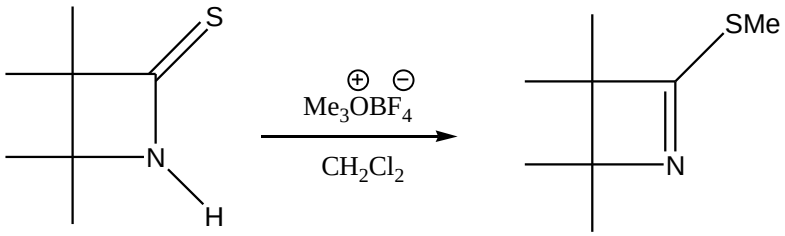
**IR $\upsilon_{max}$ (cm$^{-1}$):** 3117 (br, NH), 2988 (w), 1492 (s, C=S), 1455 (m), 1393 (w) 1367 (m), 1311 (w), 1257.

**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 8.23 (1H, bs, NH), 1.38 (6H, s, 2 x $CH_3$), 1.24 (6H, s, 2 x ($CH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 212.27 (C=S), 68.57 (C), 56.81 (C), 23.51 ($CH_3$), 20.92 ($CH_3$).

**MS (*m/z*):** 144.1 [M+H] , 166.1 [M+Na] , 309.1 [$M_2$+Na] .

### 3.2.1.6.3. Synthesis of 2-methylthio-3,34,,4-tetramethyl-1-azetine




**297** **298**

**Scheme 3.26**

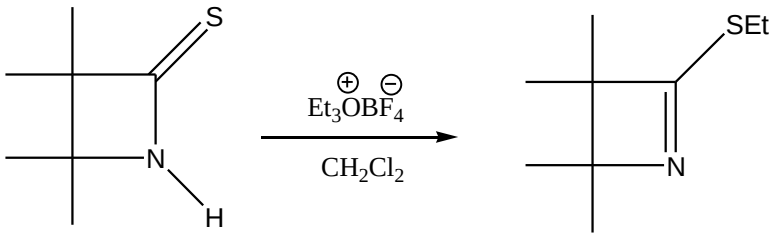
To 3,3,4,4-tetramethylazetidin-2-thione (500 mg, 3.5 mmol) was added Meerwein's reagent (620 mg, 4.19 mmol, 1.2 eq.) in dry dichloromethane (15 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added dropwise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give the product as dark orange oil, as reported previously[157].

**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 1.97 (3H, s, $SCH_3$), 1.26 (6H, s, 2 x $CH_3$), 1.12 (6H, s, 2 x $CH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 182.96 (C=N), 69.82 (C), 51.34 (C), 23.81 ($CH_3$), 20.57 ($CH_3$), 10.58 ($SCH_2CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.1.7. Synthesis of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine




**297** **299**

**Scheme 3.27**

To 3,3,4,4-tetramethylazetidin-2-thione (380 mg, 2.65 mmol) was added Meerwein's reagent (1M soln. in DCM, 3.72 mmol, 1.4 eq.) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added drop wise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^{o}$C. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated in *vacuo* to give the product as dark orange oil, as reported previously[157].

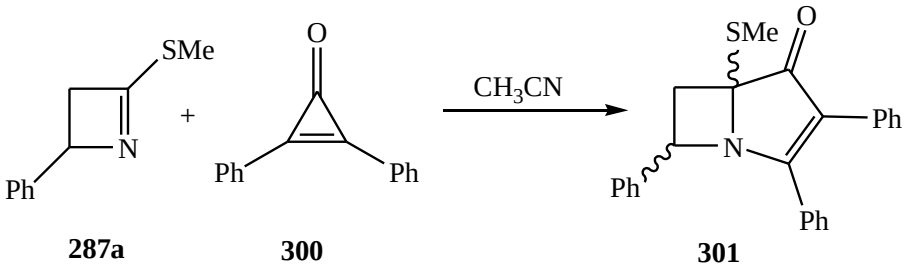
**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 2.94 (2H, q, *J*=7.3 Hz, $SCH_2CH_3$), 1.32 (3H, t, *J*=7.2 Hz ($SCH_2CH_3$), 1.25 (6H, s, 2 x $CH_3$), 1.13 (6H, s, 2 x $CH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 186.96 (C=N), 69.88 (C), 51.32 (C), 23.82 ($CH_3$), 21.75 ($CH_2$), 20.61 ($CH_3$), 14.48 ($SCH_2CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

## 3.2.2. Reactivity of 1-azetines with cyclopropenones

### 3.2.2.1. Reactivity of 2-methylthio-4-phenyl-1-azetine with diphenylcyclopropenone : Synthesis of *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one*




**287a** **300** **301**

**Scheme 3.28**

To a mixture of 4-phenyl-2-methylthio-1-azetine (300 mg, 1.69 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (348 mg, 1.69 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature for 24 h. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.21 to give the product as a yellow oil (380 mg, 59 %).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.61-6.81 (15H, m, Ph), 5.58 and 4.25 (2 x diastereo, 1H, 2 x dd, *J* = 8.1, 8.1 and 5.5, 9.6, Ph-CH-$CH_2$), 3.18 and 2.50 (2 x diastereo, 1H, 2 x dd, *J* = 9.6, 12.6 and 5.5, 12.9, Ph-CH-$CH_2$), 2.97 and 3.03 (2 x diastereo, 1H, 2 x dd, *J* = 8.1, 12.9 and 8.1, 12.6, Ph-CH-$CH_2$), 2.14 and 2.08 (2 x diastereo, 3H, s, S-$CH_3$).

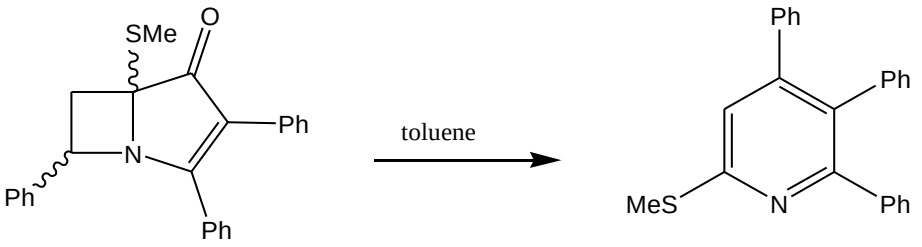
**$^{13}$C NMR: $\delta_C$ (100 MHz, $CDCl_3$)** 202.89 & 202.56 (C), 177.64 and 175.38 (C), 141.39 (C), 140.68 (CH), 135.26 (CH), 132.14 and 132.06 (C), 131.20 and 131.14 (C), 130.76 (CH), 130.35 (CH), 130.07 (C), 129.67 (CH), 129.06 and 129.03 (CH), 128.81 (CH), 128.78 (CH),

128.73 (CH), 128.68 (CH), 128.46 (CH), 128.14 (CH), 128.04 (CH), 127.89 (CH), 127.56 (CH), 127.22 (CH), 127.15 (CH), 126.33 (C), 124.03 (C), 66.63 and 66.16 (CH), 31.29 and 29.90 ($CH_2$), 11.92 and 11.69 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.2. Reactivity of *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* :

**Synthesis of *2,3,4-triphenyl-6-methylthio-1-pyridine***




**301** **302**

**Scheme 3.29**

100 mg (0.26 mmol) of *5-methylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* was added to toluene (8 ml) and the mixture was heated at reflux at 115 $^{o}$C overnight. The solvent was evaporated in vacuo and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 product was obtained as white crystals (65 mg, 71 %), m.p. 170-173 $^{o}$C.

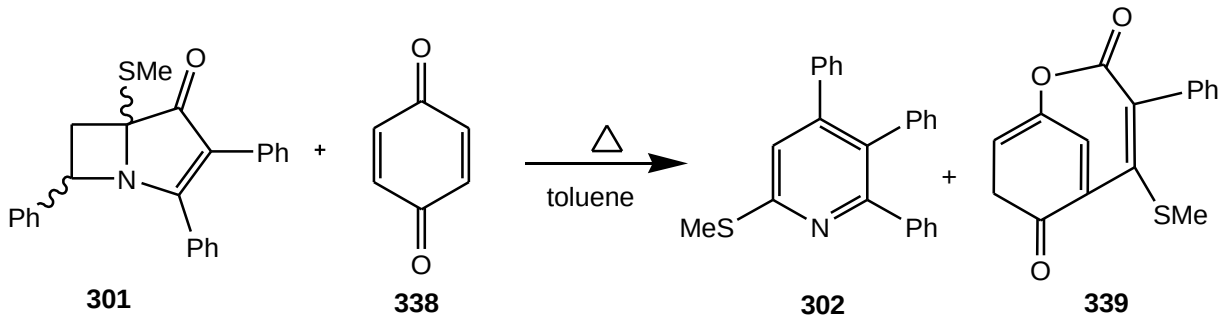
**IR: $\upsilon_{max}$ ($cm^{-1}$):** 2920 (s), 2852 (m), 1556 (s), 1519 (s), 1403 (m), 1353 (m), 1123 (m) 766 (s), 750 (m), 693 (m), 609 (m).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.35-7.30 (2H, m, Ph), 7.23 (1H, s, pyrid-H), 7.22-7.18 (6H, m, 7 x PhH), 7.09-7.04 (5H, m, 5 x Ph-H), 6.89 (1H, d, *J* = 8.0, Ph-H), 6.87 (1H, d, *J* = 8.0, Ph-H), 2.7 (3H, s, $CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 158.02 (C), 157.48 (C), 150.05 (C), 140.55 (C), 139.32 (C), 137.71 (C), 131.52 (CH), 130.24 (C), 130.09 (CH), 129.21 (CH), 127.86 (CH), 127.70 (CH), 127.48 (CH), 127.42 (CH), 127.37 (CH), 126.49 (CH), 120.98 (CH), 13.39 ($CH_3$).

**HRMS (m/z):** calc for $C_{24}H_{19}NS+H^+$ $(M+H)^+$, 354.1311, found 354.1300.

**3.2.2.3. Reactivity of *5-methylthio-2,3,7-triphenyl-1-azabicyclo(3.2.0)hept-2-en-4-one* with benzoquinone : Synthesis of *2,3,4-triphenyl-6-methylthio-1-pyridine* and *5-methylthio-4-phenyl-2-oxabicyclo[4.3.1]deca-1(9),4-diene-3,7-dione*.**




**301** **338** **302** **339**

**Scheme 3.30**

100 mg (0.27 mmol) of 5-methylthio-2,3,7-triphenyl-1-azabicyclo [3.2.0] hept-2-en-4-one and benzoquinone (58 mg, 0.54 mmol, 2 eq.) were added to toluene (8 ml) and the mixture was heated at reflux at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1) two products were obtained, one pyridine as white crystals (52 mg, 65 %) and the tentatively assigned dione **339**, (24 mg, 31 %) .

**Pyridine**

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.28 (12H, m, Ph), 7.07 (2H, d, *J*= 7.8 Hz, Ph), 6.88 (2H, d, *J*= 8.0 Hz, Ph), 2.7 (3H, s, $CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 158.8 (C-N), 157.4 (C-N), 150.04 (C (Ar)), 140.5 (C (Ar)), 139.3 (C (Ar)), 137.7 (C (Ar)), 131.5 (2C (Ar)), 130.2 (C (Ar)), 130.1 (2C (Ar)), 129.2 (2C (Ar)), 128.2 (C (Ar)), 127.88 (2C (Ar)), 127.72 (2C (Ar)), 127.50 (2C (Ar)), 127.45 (C (Ar)), 127.39 (C (Ar)), 126.5 (C (Ar)), 120.98 (C (Ar)), 13.42 (C ($S-CH_3$)).

**Dione**

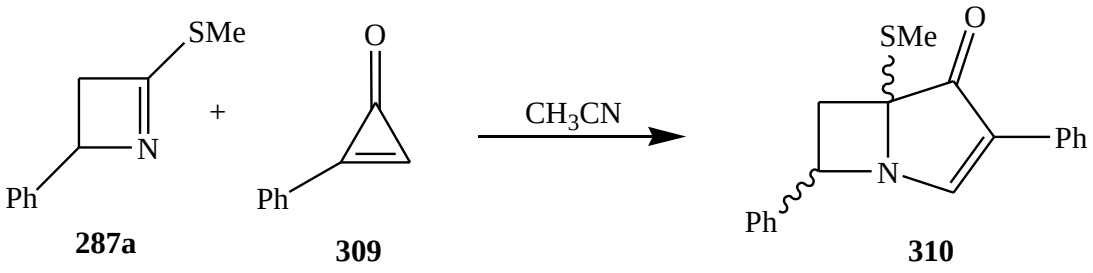
**IR $\upsilon_{max}$ ($cm^{-1}$):** 3001, 1651, 1597, 1289, 1059.

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.28 (1H, s), 7.23-7.17 (2H, m), 7.10 (1H, d, *J*= 6.1 Hz), 6.83 (1H, d, *J*= 10.1 Hz), 6.74 (1H, dd, *J*= 7.5 and 2.6 Hz), 6.12 (1H, dd, *J*= 2.4 and 2.0 Hz), 3.77 (2H, d, 1.9 Hz), 2.23 (3H, s, $SCH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 187.72 (C=O), 187.39 (C=O)), 148.31 (CH (Ar)), 136.72 (C (Ar)), 136.42 (C (Ar)), 134.25 (C (Ar)), 133.00 (C (Ar)), 130.72 (C (Ar)), 130.39 (C (Ar)), 127.50 (C (Ar)), 126.51 (C (Ar)), 32.64 ($CH_2$), 19.40 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.4. Reactivity of 2-methylthio-4-phenyl-1-azetine with phenylcyclopropenone : Synthesis of *5-methylthio-3-phenyl-1-azabicyclo [3.2.0] hept-2-en-4-one*




**287a** **309** **310**

**Scheme 3.31**

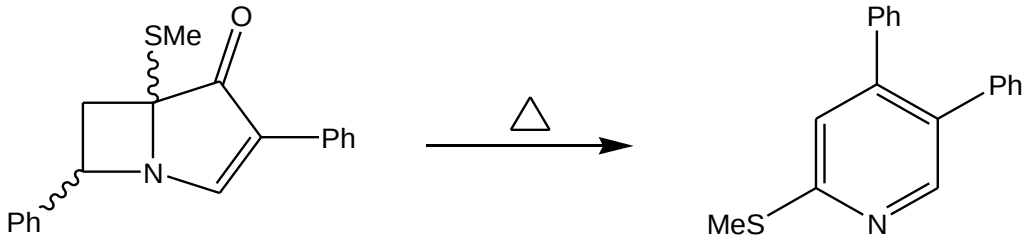
To a mixture of 4-phenyl-2-methylthio-1-azetine (200 mg, 1.13 mmol) in dry acetonitrile (10 ml) was added phenylcyclopropenone (170 mg, 1.13 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.24) to give the product as light yellow oil (122 mg, 35 %).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 8.36 and 7.76 (2 x diastereo, 1H, 2 x s, vinyl-H), 7.85 – 7.65 (3H, m, 3 x PhH), 7.50-7.26 (7H, m, 7 x PhH), 5.66 and 4.65 (2 x diastereo, 1H, 2 x dd, *J* = 7.6, 9.6 and 5.2, 10.5, Ar-CH-$CH_2$), 3.06 and 3.00 (2 x diastereo, 1H, dd, *J* = 9.6, 12.6, and 9.6, 12.4, Ar-CH-$CH_2$), 2.83 (diastereo 1, 1H, dd, *J* = 7.6, 12.4, Ar-CH-$CH_2$), 2.48 (diastereo 2, 1H, dd, *J* = 5.2, 12.6, Ar-CH-$CH_2$), 2.04 and 2.03 (2 x diastereo, 3H, s, S-$CH_3$).
**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 203.13 and 201.74 (C=O), 167.14 and 164.28 (C), 140.44 (C), 135.20 (C), 130.61 (C), 130.13 (C), 129.48 (CH), 129.14 (CH), 128.75 (CH), 128.73 (CH), 128.60 (CH), 128.45 (CH), 128.09 (CH), 127.96 (CH), 127.55 (CH), 127.27 (CH),

126.57 (CH), 126.52 (CH), 125.85 (CH), 125.56 (CH), 79.67 (CH), 65.34 (CH), 32.79 and 32.32 ($CH_2$), 12.08 and 11.55 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.5. Reactivity of *5-methylthio-3-phenyl-1-azabicyclo [3.2.0] hept-2-en-4-one* : Synthesis of *2-methylthio-4,5-diphenylpyridine*.




**310** **311**

**Scheme 3.32**

*5-Methylthio-3, 7-diphenyl-1-azabicyclo [3.2.0] hept-2-en-4-one* (120 mg, 0.39 mmol) was added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^oC$ overnight. The solvent was evaporated *in vacuo* and the mixture purified with column chromatography (PE 40-60 $^oC$ / EtOAc : 4/1). The product was obtained as white crystals (68 mg, 62 %), m.p. 153-155 $^oC$.

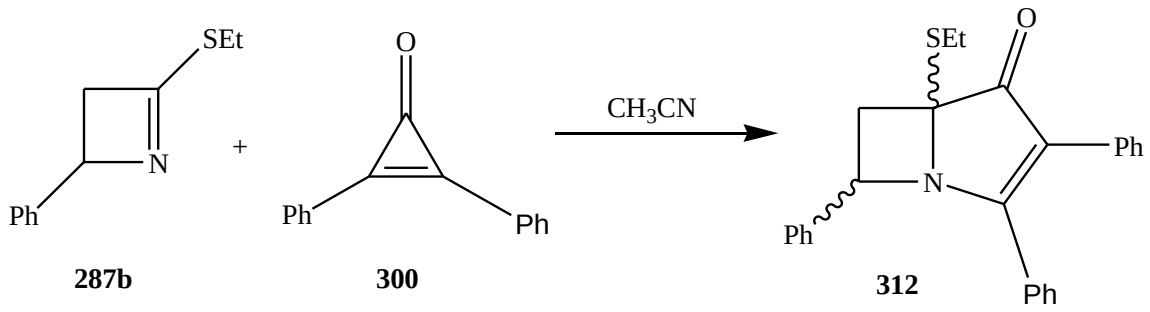
**IR $\upsilon_{max}$ ($cm^{-1}$):** 3035 (w), 3000 (w), 2910 (w), 1582 (m), 1568 (m), 1458 (m), 1443 (m), 1339 (m), 1114 (s), 762 (s), 748 (s), 696 (s), 567 (s).

**$^1$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 8.51 (1H, s, pyrid-H), 7.31 - 7.24 (7H, m, 6 x PhH + pyrid-H), 7.18 - 7.12 (4H, m, 4 x PhH), 2.68 (3H, s, S-$CH_3$), 2.31 (3H, s, $CH_3$).

**$^{13}$C NMR $\delta$ (100 MHz, $CDCl_3$)** 159.01 (C), 150.44 (CH), 147.95 (C), 138.53 (C), 137.53 (C), 131.86 (C), 129.78 (CH), 129.24 (CH), 128.27 (CH), 128.26, (CH), 127.93 (CH), 127.11 (CH), 122.00 (CH), 13.48 ($CH_3$).

**HRMS (m/z):** calculated for $C_{18}H_{15}NS+H^+$ $(M+H)^+$, 278.0998, found 278.1000

**3.2.2.6. Reactivity of 2-ethylthio-4-phenyl-1-azetine with diphenylcyclopropenone : Synthesis of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one*.**




**287b** **300** **312**

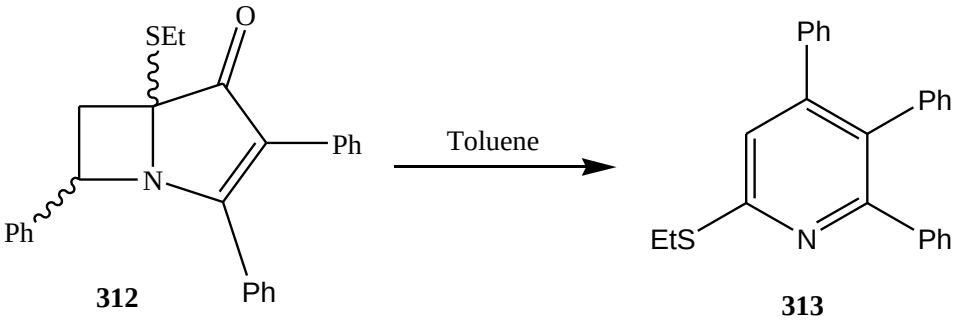
**Scheme 3.33**

To a solution of 4-phenyl-2-ethylthio-1-azetine (300 mg, 1.57 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (324 mg, 1.57 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.21 to give the product as yellow oil (380 mg, 61 %).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.65-6.90 (15H, m, Ph), 5.60 and 4.28 (2 x diastereo, 1H, 2 x dd, *J* = 8.3, 8.3 and 5.5, 9.6, Ph-CH-$CH_2$), 3.16 and 2.52 (2 x diastereo, 1H, 2 x dd, *J* = 9.6, 13.1 and 5.2, 12.6, Ph-CH-$CH_2$), 2.90 - 3.05 (2H, m, 1 x S-$CH_2CH_3$ and 1 x Ph-CH-$CH_2$ from diastereo 1), 2.56 – 2.70 (2H, m, 1x S-$CH_2CH_3$ and 1 x Ph-CH-$CH_2$ from diastereo 2), 1.23 –1.30 (2 x diastereo, 3H, 2 x t, *J* = 7.2, S-$CH_2CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 202.86 & 202.46 (C), 176.99 (C), 174.85 (C), 141.33 (C), 135.18 (C), 132.00 (CH), 131.89 (CH), 131.14 (C), 131.07 (CH), 130.64 (C), 130.52 (CH), 130.19 (CH), 130.01 (C), 129.67 (C), 129.50 (CH), 129.24 (C), 129.04 (C), 128.90 (CH), 128.86 (CH), 128.61 (CH), 128.52 (CH), 128.29 (CH), 128.12 (CH), 127.93 (CH), 127.85 (CH), 127.71 (CH), 127.36 (CH), 127.06 (CH), 127.03 (CH), 126.14 (C), 123.79 (C), 66.62 and 65.98 (CH), 35.14 and 31.86 ($CH_2$), 23.70 and 23.59 ($CH_2$), 14.59 and 14.24 ($CH_3$).
"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.7. Reactivity of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* : Synthesis of *2,3,4-triphenyl-6-ethylthio-1-pyridine*




**Scheme 3.34**

*5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.25 mmol) was added to toluene (8 ml) and the mixture was refluxed at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 the product was obtained as white crystals (68 mg, 75 %), m.p. 109-111 $^{o}$C .

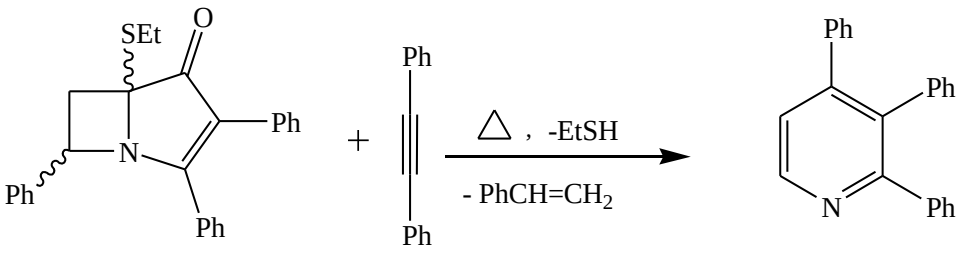
**IR: $\upsilon_{max}$ (cm$^{-1}$):** 2955, (m), 2927 (M), 2870 (m), 1561 (s), 1490 (s), 1405 (m), 1359 (s), 1219 (s), 1090 (s), 1013 (m), 824 (m), 766 (s), 697 (s), 611 (m).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.39-7.32 (2H, m, 2 x PhH), 7.28 – 7.18 (8H, m, 7 x PhH plus pyrid-H), 7.16-7.7.07 (4H, m, 4 x PhH), 6.98-6.92 (2H, m, 2 x PhH), 3.32 (2H, q, *J* = 7.3, S-$CH_2$-$CH_3$), 1.51 (3H, t, *J* = 7.3, S-$CH_2$-$CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 157.52 (C), 150.07 (C), 140.63 (C), 139.33 (C), 137.77 (C),131.54 (CH), 130.29 (CH), 129.25 (CH), 128.52 (CH), 127.98 (CH), 127.88 (CH), 127.74 (CH), 127.49 (CH), 127.41 (CH), 127.38 (CH), 126.51 (C), 121.62 (C), 24.52 ($CH_2$), 15.0 (S-$CH_3$).

**HRMS (m/z):** calc for $C_{25}H_{21}NS+H^+$ $(M+H)^+$, 368.1467, found 368.1460.

### 3.2.2.8. Reactivity of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* with diphenyl acetylene : Synthesis of 2,3,4-triphenyl-1-pyridine




**312** **335** **336**

**Scheme 3.35**

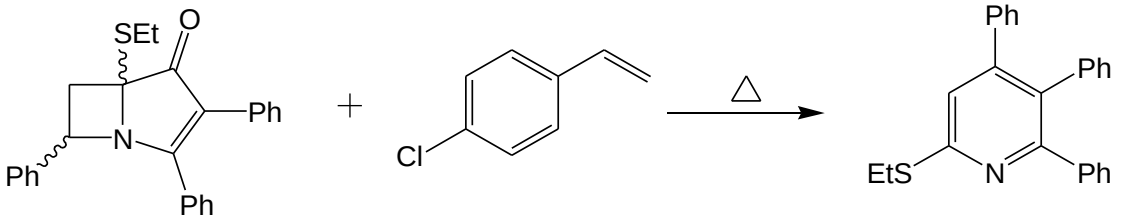
*5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (50 mg, 0.13 mmol) and diphenylacetylene (111 mg, 0.63 mmol, 4 eq.) were added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^{o}$C overnight. The solvent was evaporated in vacuo and after purification with column chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1) the product was obtained as yellow crystals (20 mg, 50 %).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 8.75 (1H, d, *J*= 7.3 Hz), 7.36 (1H, d, *J*= 6.3 Hz), 7.30-7.27 (3H, m, Ph-H), 7.24-7.20 (6H, m, Ph-H), 7.10-7.05 (4H, m, Ph-H), 6.90 (2H, dd, *J*= 7.8 and 1.8 Hz, Ph-H).

**$^{13}$C NMR $\delta$ (125 MHz, $CDCl_3$)** 158.38 (C-N), 149.38 (C-N)), 148.26 (CH (Ar)), 140.70 (C (Ar)), 139.35 (C (Ar)), 137.70 (C (Ar)), 134.37 (2C (Ar)), 131.27 (C (Ar)), 129.85 (2C (Ar)), 129.35 (2C (Ar)), 128.37 (C (Ar)), 127.93 (2C (Ar)), 127.73 (2C (Ar)), 127.62 (2C (Ar)), 127.39 (C (Ar)), 127.37 (C (Ar)), 126.66 (C (Ar)), 123.69 (C (Ar)).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.9. Reactivity of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* with 4-chlorostyrene : Synthesis of *2,3,4-triphenyl-6-ethylthio-1-pyridine*



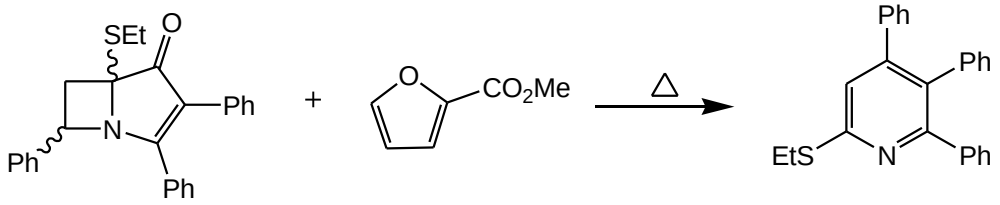

**312** **334** **313**

**Scheme 3.36**

5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one (100 mg, 0.25 mmol) and chlorostyrene (63.5 µl, 0.50 mmol, 2 eq.) were added to *o*-xylene (8 ml) and the mixture was refluxed at 155 $^{o}$C overnight. The solvent was evaporated *in vacuo* and the mixture was purified with column chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1) to give 2,3,4-triphenyl-6-ethylthio-1-pyridine as the only product.

Data as above for the same compound.

### 3.2.2.10 Reactivity of *5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* with methylfurate : Synthesis of *2,3,4-triphenyl-6-ethylthio-1-pyridine*



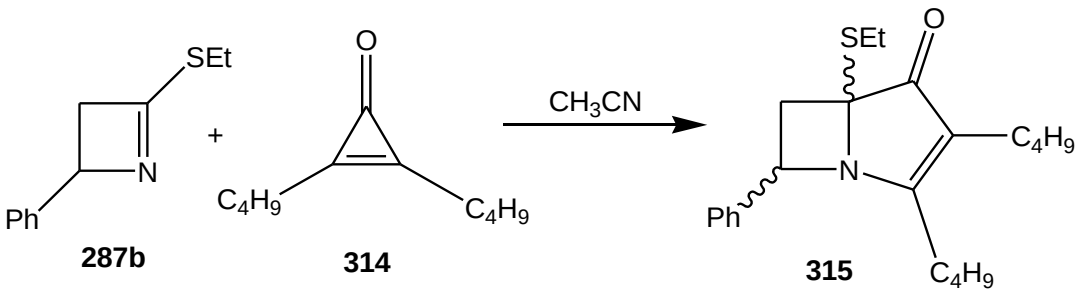

**313** **338** **314**

**Scheme 3.37**

*5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.27 mmol) and methylfurate (172 µl, 1.07 mmol, 4 eq.) were added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after

purification with column chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1), the pyridine product was obtained as white crystals (80 mg, 75 %). No other products were isolated. Data for the pyridine was identical to that reported as above for the same compound.

### 3.2.2.11. Reactivity of 2-ethylthio-4-phenyl-1-azetine : Synthesis of *5-ethylthio-2,3-dibutyl-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one*




**Scheme 3.38**

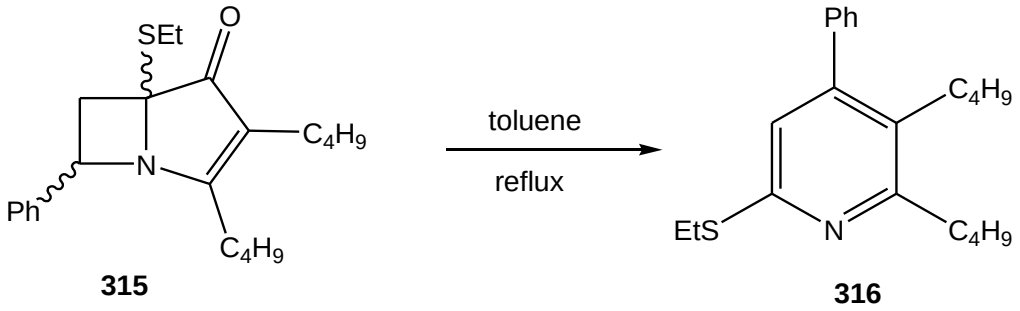
To a mixture of 4-phenyl-2-ethylthio-1-azetine (300 mg, 1.56 mmol) in dry acetonitrile (10 ml) was added dibutylcyclopropenone (322 mg, 1.56 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.21 to give the product as dark yellow oil (318 mg, 57 %).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.59 (1H, d, *J* = 7.4, Ph), 7.45-7.28 (3H, m, Ph), 7.22 (1H, d, *J* = 7.4, Ph), 5.48 (diastero 1, 1H, dd, *J* = 8.5, 8.5, Ph-*CH*-$CH_2$), 4.3 (diastereo 2, 1H, dd, *J* = 5.4 and 8.7, Ph-*CH*-$CH_2$), 2.89 (diastereo 1, 1H, dd, *J* = 15.6, 8.5, $CHCH_2$), 2.62-2.50 (1H, m, $CH_2$), 2.49-2.40 (2H, m, $CH_2$), 2.34-2.28 (1H, dd, *J* = 14.8, 5.4, $CH_2$), 2.22-2.13 (2H, m, $CH_2$), 2.04- 2.00 (diastereo 1, 1H, dd, *J* = 8.5, 12.5, $CH_2$), 1.99-1.94 (diastereo 2, 1H, dd, *J* = 8.5, 12.5, $CH_2$), 1.56-1.48 (2H, m, $CH_2$), 1.42-1.27 (6H, m, 3 x $CH_2$), 1.21-1.17 (3H, 2 x t, both diastereo, *J* = 7.4, $CH_3$), 0.94 (diastereo 1, 3H, t, *J* = 7.0, $CH_3$), 0.92 (diastereo 2, 3H, t, *J* = 7.0, $CH_3$), 0.86 (diastereo 1, 3H, t, *J* = 7.3, $CH_3$), 0.77 (diastereo 2, 3H, t, *J* = 7.2, $CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 205.44 and 204.96 (C=O), 182.78 and 180.98 (C), 141.71 (C), 136.29 (C), 129.31 (CH), 128.90 (CH), 128.69 (CH), 128.61 (CH), 128.33 (C), 128.06 (C), 127.68 (CH), 127.26 (C), 126.47 (CH), 126.22 (C), 75.45 and 75.11 (CH), 64.94 and 64.58 ($CH_2$), 33.88, 31.88, 31.29, 31.09, 29.96, 29.93, 29.24, 27.70 (8 x $CH_2$), 23.12, 22.77, 22.73, 22.63, 22.55, 22.49 (6 x $CH_2$), 14.62, 14.47, 13.96, 13.93, 13.73, 13.65 (6 x Me).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.12. Reactivity of *5-ethylthio-2,3-dibutyl-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* : Synthesis of *2,3-dibutyl-4-phenyl-6-ethylthio-1-pyridine*




**315** **316**

**Scheme 3.39**

*5-ethylthio-2,3-dibutyl-4-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.28 mmol) was added to toluene (8 ml) and the mixture was refluxed at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 product was obtained as a clear oil (67 mg, 73 %).

**IR $\upsilon_{max}$ ($cm^{-1}$):** 2955 (s), 2925 (s), 2867 (m), 1569 (s), 1531 (m), 1456 (m), 1368 (m), 1120 (w), 1075 (w), 962 (m), 824 (m), 766 (m), 700 (s).

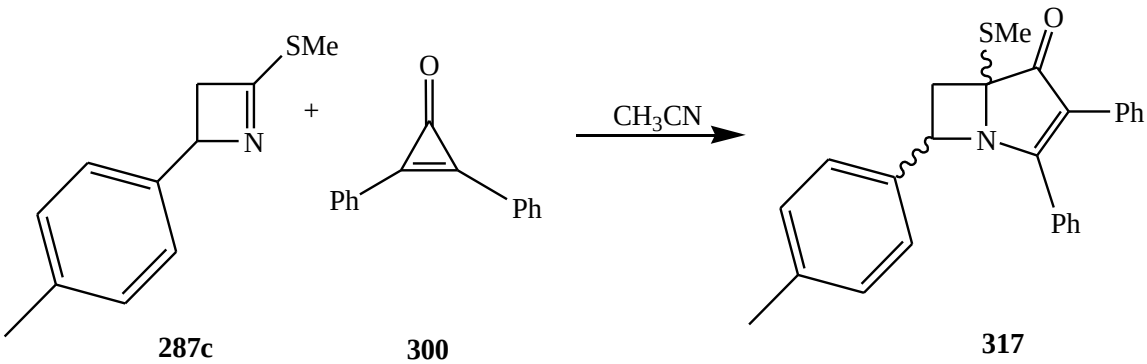
**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.45-7.35 (3H, m, 3 x PhH), 7.31-7.23 (2H, m, 2 x PhH), 6.84 (1H, s, pyrid-H), 3.2 (2H, q, *J* = 7.3, S-$CH_2$-$CH_3$), 2.82 (2H, dd, *J* = 7.5 and 11.4, $CH_2$), 2.54-2.47 (2H, m, $CH_2$), 1.83-1.76 (2H, m, $CH_2$), 1.45 (2H, q, *J* = 7.5, $CH_2$), 1.4 (3H, t, *J* =

7.3, S-$CH_2$-$CH_3$), 1.35-1.28 (2H, m, $CH_2$), 1.2 (2H, q, *J* = 7.3, $CH_2$), 1.0 (3H, t, *J* = 7.3, $CH_3$), 0.78 (3H, t, *J* = 7.3, $CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 160.67 (C), 154.16 (C), 150.42 (C), 140.26 (C), 129.16 (C),128.48 (CH), 128.11 (CH), 127.48 (CH), 120.35 (CH), 34.62 ($CH_2$), 32.93 ($CH_2$), 31.58 $CH_2$), 29.73 ($CH_3$), 24.55 ($CH_2$), 22.88 ($CH_2$), 22.78 ($CH_2$), 14.98 ($CH_3$), 14.16 ($CH_2$), 13.62 ($CH_3$).

**HRMS (m/z):** calc for $C_{21}H_{29}NS+H^+$ $(M+H)^+$, 328.2093, found 328.2086.

### 3.2.2.13. Reactivity of *2-methylthio-4-tolyl-1-azetine* : Synthesis of *5-methylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one*




**287c** **300** **317**

**Scheme 3.40**

To a solution of *4-tolyl-2-methylthio-1-azetine* (300 mg, 1.56 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (322 mg, 1.56 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^oC$ / EtOAc : 4/1, Rf = 0.21 to give the product as a yellow oil (388 mg, 63 %).

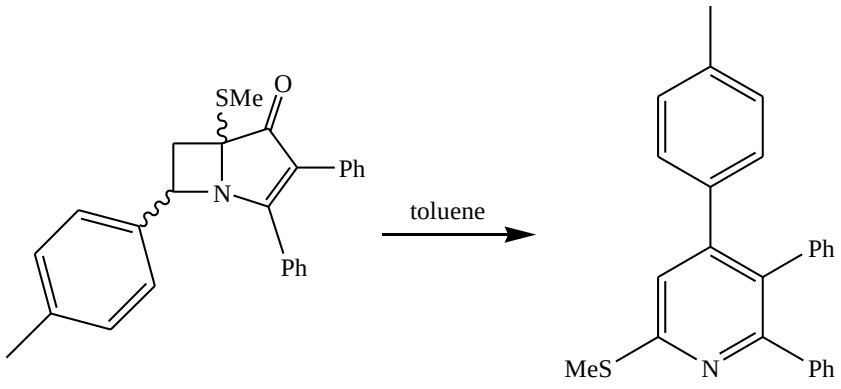
**$^1$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.53 – 7.32 (10H, m, PhH), 6.98 and 6.75 (2 x diastereo, 2H, 2 x d, *J* = 8.1 and 8.1, Tol), 7.25 and 6.79 (2 x diastereo, 2H, 2 x d, *J* = 8.1 and 8.1, Tol), 5.54 and 4.27 (2 x diastereo, 1H, 2 x dd, *J* = 8.1, 8.1 and 8.5, 5.1, ArCH), 3.16 and 2.49 (2 x diastereo, 1H, 2 x dd, *J* = 12.8, 9.6 and 12.8, 5.1, ArCH$CH_2$), 3.02 and 2.95 (2 x diastereo,

1H, 2 x dd, *J* = 8.1, 12.8 and 12.8, 8.5, ArCHCH$_2$), 2.41, 2.14, 2.12 and 2.07 (2 x diastereo, 6H, 4 x s, ArMe and SMe).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 202.83 and 202.46 (C=O), 177.56 and 177.52 (C), 138.44 and 138.29 (C), 137.69 (C), 132.18 (C), 132.03 (C), 131.92 (CH), 131.08 (C), 131.03 (CH), 130.46 (CH), 130.23 (CH), 129.96 (C), 129.52 (CH), 129.31 (CH), 128.87 (CH), 128.75 (CH), 128.60 (CH), 128.50 (CH), 128.44 (CH), 128.27 (CH), 128.12 (C), 127.52 (CH), 127.35 (CH), 126.99 (CH), 126.95 (CH), 126.21 (C), 123.75 (C), 66.38 and 65.92 (CH), 34.35 and 31.01 ($CH_2$), 21.29 and 20.94 ($CH_3$), 11.76 and 11.52 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.14. Reactivity of *5-methylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* : Synthesis of *2,3-diphenyl-4-tolyl-6-methylthio-1-pyridine*




**317** **318**

**Scheme 3.41**

*5-Methylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.25 mmol) was added to toluene (8 ml) and the mixture was heated at reflux at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 the product was obtained as white crystals (69 mg, 74 %), m.p. 179-182 $^{o}$C.

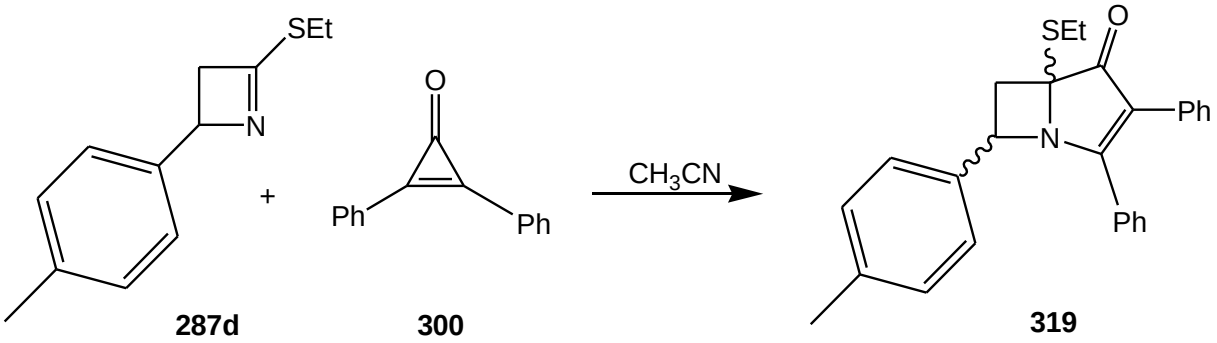
**IR $\upsilon_{max}$ ($cm^{-1}$):** 2918 (s), 2849 (m), 1560 (m), 1506 (m), 1410 (m), 1355 (s), 1120 (s), 1028 (m), 818 (s), 765 (s), 697 (s), 612 (m).

**$^1$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.34 - 7.30 (3H, m, 3 x PhH), 7.24 - 7.18 (4H, m, 3 x PhH + pyrid-H), 7.08 (2H, d, *J* = 7.8, 2 x PhH), 7.02 (2H, d, *J* = 8.1, 2 x Tol-H), 6.96 (2H, d, *J* = 8.1, 2 x Tol-H), 6.88 (2H, dd, *J* = 1.8 and 6.0, 2 x PhH), 2.68 (3H, s, S-$CH_3$), 2.31 (3H, s, Ar$CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 157.97 (C), 157.50 (C), 149.99 (C), 140.64 (C), 137.86 (C), 137.20 (C), 136.32 (C), 131.54 (CH), 130.22 (C), 130.09 (CH), 129.13 (CH), 128.61 (CH), 127.73 (CH), 127.47 (CH), 127.37 (CH), 126.44 (CH), 121.03 (CH), 21.18 ($CH_3$), 13.42 ($CH_3$).

**HRMS (m/z):** calc for $C_{25}H_{21}NS+H^+$ $(M+H)^+$, 368.1467, found 368.1468

### 3.2.2.15. Reactivity of *2-ethylthio-4-tolyl-1-azetine* : Synthesis of *5-ethylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one*




**Scheme 3.42**

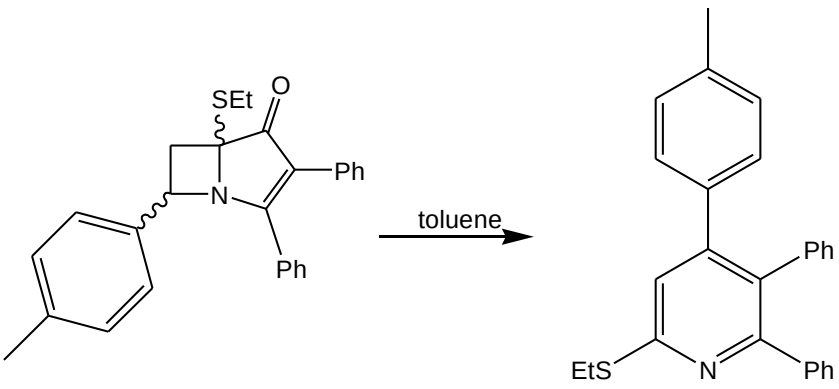
To a solution of *4-tolyl-2-ethylthio-1-azetine* (300 mg, 1.46 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (301 mg, 1.46 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^oC$ / EtOAc : 4/1, Rf = 0.21 to give the product as a yellow oil (394 mg, 66 %).

**$^1$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.52-7.12 (10H, m, 2 x Ph), 7.01, 6.94, 6.78, 6.72 (4H, 4 x d, *J* = 8.2, 8.2, 8.1, 8.1, Tol: 2 x diastereo), 5.57 and 4.26 (2 x diastereo, 1H, 2 x dd, *J* = 8.4, 8.4 and 9.6, 5.4, ArCH), 3.16 (diastereo 2, 1H, dd, *J* = 12.6 and 9.6, Ar-CH-C*H*H), 3.01 (diastereo 1, 1H, dd, *J* = 13.1, 8.0, ArCHCH*H*), 2.93 (diastereo 1, 1H, dd, *J* = 8.4, 13.1, Ar-CH-CHH), 2.65 (diastereo 2, 1H, dd, *J* = 12.6, 5.4, Ar-CH-CHH), 2.47-2.70 (2 x diastereo, 2H, m, S-$CH_2CH_3$), 2.41 and 2.11 (2 x diastereo, 3H, 2 x s, Ar$CH_3$), 1.30 and 1.28 (2 x diastereo, 3H, 2 x t, *J* = 7.2, 7.2, S-$CH_2$-$CH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 202.95 and 202.50 (C=O), 177.08 and 175.15 (C), 138.40 (C), 137.64 (C), 136.69 (C), 132.26 (C), 132.11 (C), 131.22 (C), 131.13 (C), 130.66 (CH), 130.44 (CH), 130.23 (CH), 130.04 (C), 129.73 (C), 129.67 (CH), 129.51 (CH), 129.30 (CH), 128.87 (CH), 128.76 (CH), 128.60 (CH), 128.51 (CH), 128.43 (CH), 128.28 (CH), 128.12 (CH), 127.53 (CH), 127.28 (C), 127.00 (CH), 126.97 (CH), 126.14 (C), 123.65 (C), 66.54 and 65.92 (CH), 35.15 and 31.74 ($CH_2$), 23.70 and 23.57 ($CH_2$), 21.29 and 20.95 ($CH_3$), 14.63 and 14.60 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.16. Reactivity of *5-ethylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one :* Synthesis of *2,3-diphenyl-4-tolyl-6-ethylthio-1-pyridine*




**319** **320**

**Scheme 3.43**

*5-Ethylthio-2,3-diphenyl-7-tolyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.24 mmol) was added to toluene (8 ml) and the mixture was heated at reflux at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 the product was obtained as white crystals (66 mg, 72 %), 140-143 $^{o}$C.

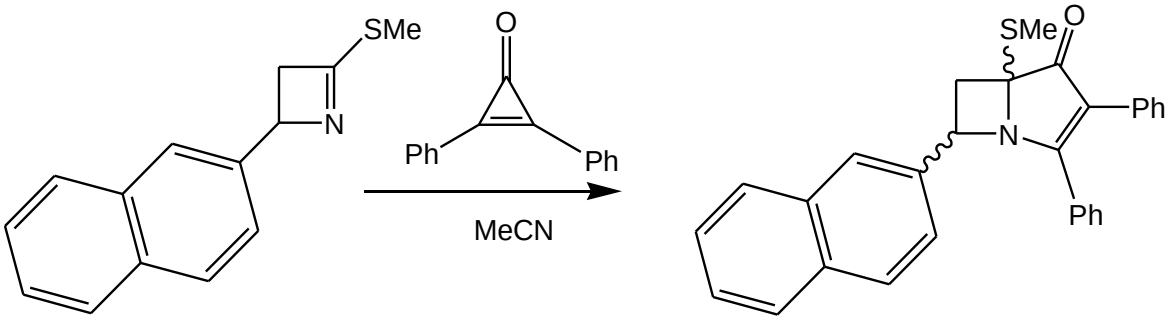
**IR $\upsilon_{max}$ (cm$^{-1}$):** 2981 (m), 1556 (m), 1508 (m), 1365 (m), 1124 (m), 819 (s), 763 (m), 697 (s).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.36-7.34 (2H, m, 2 x PhH), 7.23-7.18 (4H, m, 3 x PhH + Pyrid-H), 7.12 – 7.06 (3H, m, 3 x Ph), 7.02 (2H, d, *J* = 8.2, 2 x Tol-H), 6.97 (2H, d, *J* = 8.2, 2 x Tol-H), 6.90 (2H, dd, *J* = 8.0 and 1.8, 2 x PhH), 3.3 (2H, q, *J* = 7.3, S-$CH_2$-$CH_3$), 2.31 (3H, s, Ar$CH_3$) 1.5 (3H, t, *J* = 7.3, S-$CH_2$-$CH_3$) .

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 157.53 (C), 157.44 (C), 150.02 (C), 140.73 (C), 137.93 (C), 137.16 (C), 136.35 (C), 131.56 (CH), 130.29 (C), 130.10 (CH), 129.15 (CH), 128.61 (CH), 127.74 (CH), 127.45 (CH), 127.32 (CH), 126.44 (CH), 121.68 (CH), 24.52 ($CH_2$), 21.19 ($CH_3$), 14.99 ($CH_3$).

**HRMS (m/z):** calc for $C_{26}H_{23}NS+H^+$ $(M+H)^+$, 382.1624, found 382.1624.

### 3.2.2.17. Reactivity of *2-methylthio-4-naphthyl-1-azetine* : Synthesis of *5-methylthio-2,3-diphenyl-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one*




**287e** **321**

**Scheme 3.44**

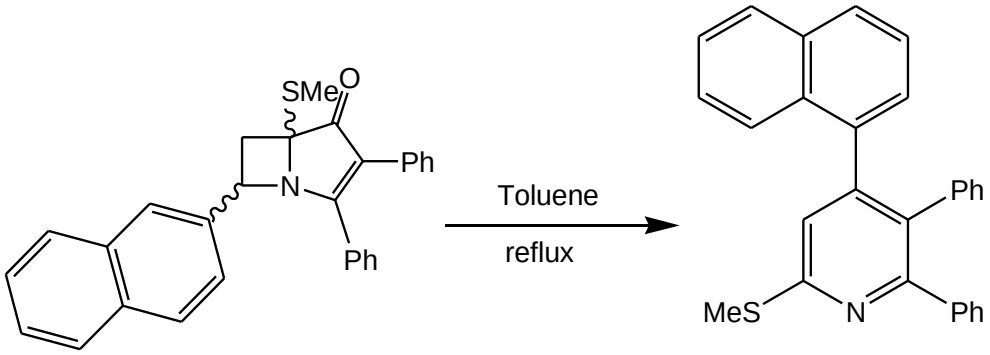
To a solution of *4-naphthyl-2-methylthio-1-azetine* (200 mg, 0.88 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (181 mg, 0.88 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent was evaporated *in vacuo* and mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.23 to give the product as a yellow oil (192 mg, 51 %).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.98-7.85 (2H, m, Ar), 7.60-7.15 (10H, m, Ar), 7.0 (1H, dd, *J* = 1.7 and 8.4, Ar), 6.92 (2H, dd, *J* = 7.1 and 16.1, Ar), 6.72 (2H, dd, *J* = 7.6, 7.6, Ar), 5.74 (diastereo 1, 1H, dd, *J* = 8.3 and 8.3, Ph-CH-$CH_2$), 4.48 (diastereo 2, 1H, dd, *J* = 5.5 and 8.7, Ph-CH-$CH_2$), 3.26 (diastereo 1, 1H, dd, *J* = 9.6 and 12.6, Ph-CH-$CH_2$), 3.18 (diastereo 2, 1H, dd, *J* = 8.0 and 13.1, Ph-CH-$CH_2$), 3.06 (diastereo 1, 1H, dd, *J* = 8.3 and 13.1, Ph-CH-$CH_2$), 2.59 (diastereo 2, 1H, dd, *J* = 5.5 and 12.6, Ph-CH-$CH_2$), 2.13 and 2.07 (both diastereo, 3H, 2 x s, S-$CH_3$).

**$^{13}$C NMR $\delta$ (100 MHz, $CDCl_3$)** 202.78 and 202.40 (C=O), 177.43 and 175.45 (C), 138.65 (C), 133.19 (C), 133.06 (C), 132.89 (C), 132.43 (C), 132.39 (C), 131.97 (C), 131.84 (CH), 131.07 (C), 130.74 (C), 130.60 (C), 130.48 (C), 130.21 (CH), 129.93 (CH), 129.29 (CH), 128.90 (C), 128.69 (CH), 128.65 (CH), 128.63 (CH), 128.56 (CH), 128.54 (CH), 128.29 (CH), 128.18 (CH), 128.01 (CH), 127.84 (CH), 127.81 (CH), 127.69 (CH), 127.46 (CH), 127.43 (CH), 127.40 (CH), 127.27 (CH), 127.02 (CH), 126.47 (CH), 126.37 (CH), 126.25 (CH), 126.19 (CH), 126.04 (CH), 126.00 (C), 124.84 (CH), 123.95 (C), 66.66 and 66.22 (CH), 34.37 and 30.98 ($CH_2$), 11.79 and 11.59 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.2.2.18. Reactivity of *5-methylthio-2,3-diphenyl-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one :* Synthesis of *2,3-diphenyl-4-naphthyl-6-methylthio-1-pyridine*




**321** **322**

**Scheme 3.45**

*5-Methylthio-2,3-diphenyl-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one* (100 mg, 0.23 mmol) was added to toluene (8 ml) and the mixture was heated at reflux at 115 $^{o}$C overnight. The solvent was evaporated *in vacuo* and after purification with column chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1 the product was obtained as white crystals (59 mg, 64 %), m.p. 190-193 $^{o}$C .

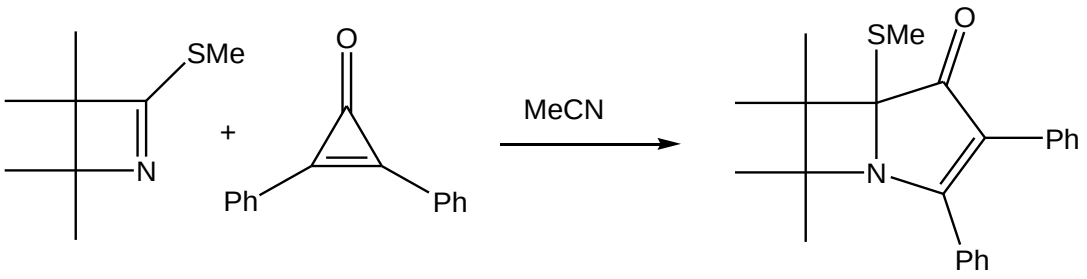
**IR $\upsilon_{max}$ (cm$^{-1}$):** 2957 (s), 2922 (s), 2854 (m), 1553 (m), 1508 (m), 1462 (m), 1271 (s), 1119 (s), 1071 (m), 962 (m), 824 (m), 743 (s), 690 (s), 671 (s).

**$^{1}$H NMR: $\delta_H$ (400 MHz, $CDCl_3$)** 7.82-7.74 (2H, m, 2 x ArH), 7.71 (1H, d, *J* = 1.3, pyrid-H), 7.59 (1H, d, *J* = 8.5, 1 x ArH), 7.48 (2H, m, 2 x ArH), 7.34 – 7.38 (3H, m, 3 x ArH), 7.19 – 7.24 (3H, m, 3 x ArH), 7.00 – 7.07 (4H, m, 4 x ArH), 6.92 (2H, dd, *J* = 1.6 and 6.7, 2 x ArH), 2.7 (3H, s, $SCH_3$).

**$^{13}$C NMR $\delta$ (100 MHz, $CDCl_3$)** 158.13 (C), 157.58 (C), 149.90 (C), 140.56 (C), 137.66 (C), 137.01 (C), 133.00 (C), 132.33 (C), 131.57 (CH), 130.32 (C), 130.14 (CH), 128.39 (CH), 28.09 (CH), 127.83 (CH), 127.62 (CH), 127.52 (CH), 127.47 (CH), 127.18 (CH), 127.10 (CH), 126.57 (CH), 126.32 (CH), 126.22 (CH), 121.31 (CH), 13.42 ($CH_3$).

**HRMS (m/z):** calc for $C_{28}H_{21}NS+H^+$ $(M+H)^+$, 404.1467, found 404.1479

### 3.2.2.19. Reactivity of 2-methylthio-3,3,4,4-teramethyl-1-azetine : Synthesis of 5-methylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo [3.2.0] hept-2-en-4-one




**298** **300** **323**

**Scheme 3.46**

To a mixture of 3,3,4,4-tetramethyl-2-methylthio-1-azetine (300 mg, 1.91 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (394 mg, 1.91 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent was evaporated *in vacuo* and mixture was purified by silica gel chromatography (PE 40-60 $^oC$ / EtOAc : 4/1, Rf = 0.23) to give the product as a yellow solid (427 mg, 62 %), m.p. 154-157 $^oC$.

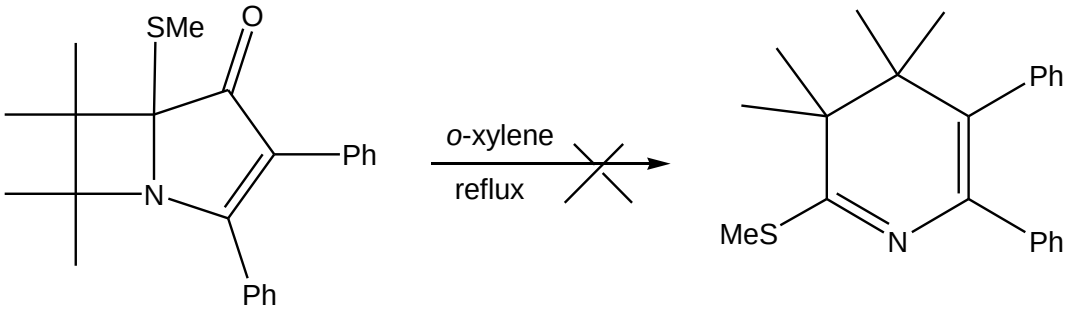
**$^1$H NMR δ (400 MHz) ($CDCl_3$)** 7.54 (2H, d, *J*= 7.1 Hz, Ar), 7.44 (2H, dt, *J*= 7.4, 1.2 Hz, Ar), 7.33 (2H, t, *J*= 7.8 Hz, Ar), 7.27 (2H, d, *J*= 4.2 Hz, Ar), 7.22-7.19 (2H, m, Ar), 1.95 (3H, s, $SCH_3$), 1.69 (3H, s, $CH_3$), 1.33 (3H, s, $CH_3$), 1.26 (3H, s, $CH_3$), 0.73 (3H, s, $CH_3$).

**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 202.31 (C=O), 175.63 (C), 133.55 (C), 131.37 (C), 131.28 (CH), 129.47 (CH), 128.84 (CH), 128.53 (CH), 128.22 (CH), 126.68 (CH), 123.57 (C), 83.79 (C), 70.30 (C), 41.93 (C), 27.96 ($CH_3$), 23.19 ($CH_3$), 22.54 ($CH_3$), 19.66 ($CH_3$), 10.60 ($SCH_3$).

**MS. (ESI, m/z),** 386.15 $(M+Na)^+$.

**HRMS (m/z):** 386.1549 calculated for $C_{23}H_{25}NNaOS$, $(M+Na)^+$, found 386.1531.

### 3.2.2.20. Reactivity of 5-methylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo [3.2.0] hept-2-en-4-one : attempted synthesis of 2,3-diphenyl-4,4,5,5-tetramethyl-6-methylthio-1-pyridine.

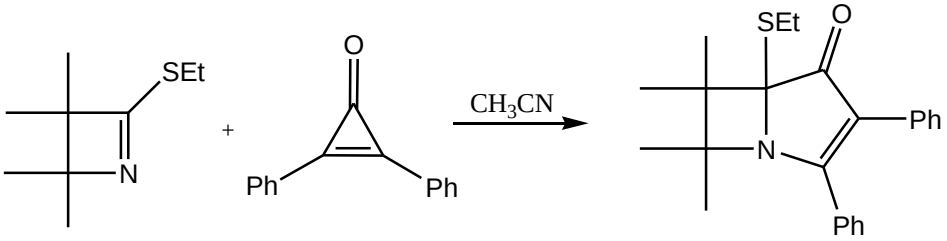



**323** **324**

**Scheme 3.47**

5-Methylthio-2,3-diphenyl—6,6,7,7-tetramethyl-1-azabicyclo[3.2.0]hept-2-en-4-one (100 mg, 0.27 mmol) was added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^{o}$C overnight. The reaction was monitored on TLC and even after 72 hours of reflux no product could be identified.

### 3.2.2.21. Reactivity of 2-ethylthio-3,3,4,4-teramethyl-1-azetine : Synthesis of 5-ethylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo [3.2.0] hept-2-en-4-one




**299** **300** **325**

**Scheme 3.48**

To a solution of 3,3,4,4-tetramethyl-2-ethylthio-1-azetine (300 mg, 1.75 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (362 mg, 1.75 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature overnight. The solvent

was evaporated *in vacuo* and the mixture was purified by silica gel chromatography (PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.23) to give the product as a yellow solid (262 mg, 40 %), m.p. 162-165 $^{o}$C.

**IR $\upsilon_{max}$ (cm$^{-1}$):** 2953, 2924, 1671, 1533, 1447, 1373, 1242, 1174.

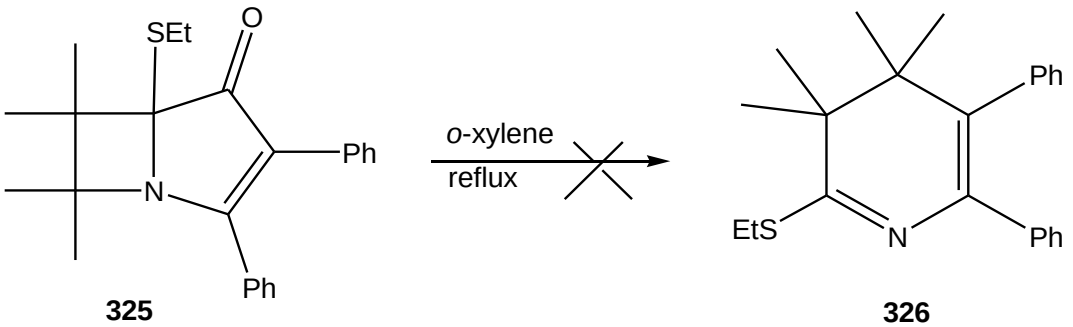
**$^{1}$H NMR δ (400 MHz) ($CDCl_3$)** 7.53 (2H, d, *J*= 7.0 Hz, ArH), 7.44 (2H, dt, *J*= 7.4, 1.3 Hz, ArH), 7.33 (2H, t, *J*= 7.7 Hz, ArH), 7.28 (2H, d, *J*= 5.6 Hz, ArH), 7.22-7.18 (2H, m, ArH), 2.57-2.36 (2H, m, $CH_2$), 1.70 (3H, s, $CH_3$), 1.31 (3H, s, $CH_3$), 1.24 (3H, s, $CH_3$), 1.18 (3H, t, *J*= 7.5 Hz, $CH_3$), 0.73 (3H, s, $CH_3$).

**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 202.40 (C=O), 175.23 (C), 133.62 (C), 131.38 (C), 131.24 (CH), 129.48 (CH), 128.84 (CH), 128.54 (CH), 128.23 (CH), 126.64 (CH), 123.33 (C), 84.26 (C), 70.23 (C), 42.35 (C), 27.99 ($CH_2$), 23.09 ($CH_3$), 22.60 ($CH_3$), 22.41 ($CH_3$), 19.71 ($CH_3$), 14.40 ($CH_3$).

**MS. (ESI, m/z),** 400.17 $(M+Na)^{+}$.

**HRMS (m/z):** 400.1706 calculated for $C_{24}H_{27}NNaOS$, $(M+Na)^{+}$, found 400.1707.

### 3.2.2.22. Reactivity of 5-ethylthio-2,3-diphenyl-6,6,7,7-tetramethyl-1-azabicyclo [3.2.0] hept-2-en-4-one : attempted synthesis of 2,3-diphenyl-4,4,5,5-tetramethyl-6-ethylthio-1-pyridine.




**325** **326**

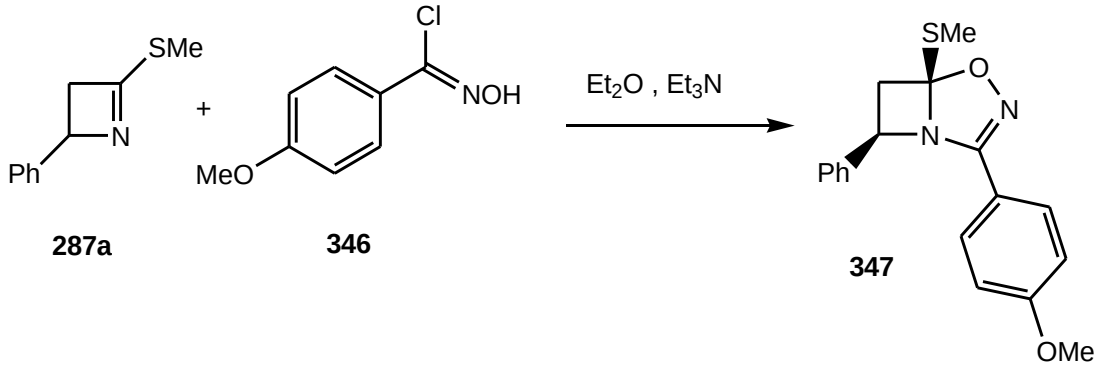
**Scheme 3.49**

5-Ethylthio-2,3-diphenyl—6,6,7,7-tetramethyl-1-azabicyclo [3.2.0] hept-2-en-4-one (100 mg, 0.26 mmol) was added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^{o}$C

overnight. The reaction was monitored on TLC and even after 72 hours of reflux no product could be identified.

## 3.2.3. Reactivity of 1-azetines with nitrile oxides

### 3.2.3.1. Synthesis of *2-(p-methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**287a** **346** **347**

**Scheme 3.50**

To a mixture of 2-methylthio-4-phenyl-1-azetine (180 mg, 1.01 mmol) and 4-methoxybenzohydroximoylchloride (1 eq. 188 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 102 mg, 134.2 µl) diluted in dry diethyl ether (30 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.31) to give a yellow oil as product, 141 mg, 43 %.

**IR $\upsilon_{max}$ (cm$^{-1}$)** 2905 (w), 1606 (s) 1510 (s), 1421 (m), 1347 (m), 1305 (m), 1256 (s), 1172 (m), 1026 (m), 836 (m), 753 (m).

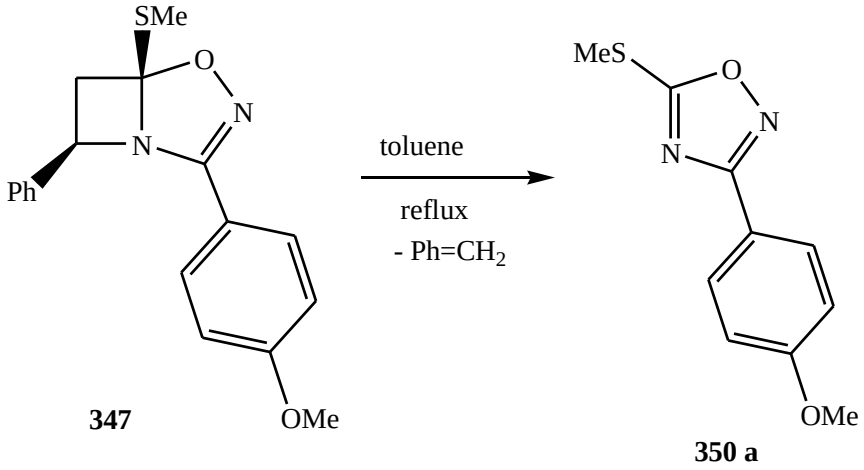
**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 7.64-7.38 (5H, m, Ph), 6.97 (2H, d, *J*=7.0 Hz, Ar), 6.82 (2H, d, *J*=7.0 Hz, Ar), 4.83 (1H, dd, *J*=5.3, 9.3 Hz, PhC*H*), 3.8 (3H, s, $OCH_3$), 3.67 (1H, dd, *J*=9.3, 13.2 Hz, PhCHC$H_2$), 2.72 (1H, dd, *J*=13.2 and 5.3 Hz, PhCHC$H_2$), 2.2 (3H, s, SC$H_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 161.7 (N=C-N), 160.6 (C, Ar), 140.6 (C, Ar), 137.5 (C, Ar), 133.9 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 126.9 (CH, Ar), 114.6 (CH, Ar), 114.4 (*C*-SMe), 66.5 (CH), 55.3 ($OCH_3$), 44.6 ($CH_2$), 10.3 ($SCH_3$).

**MS (*m/z*)** 349.1 $[M+Na]^+$, 675.2 $[M_2 + Na]^+$.

**HRMS *(m/z)*** $[M+Na]^+$ for $C_{18}H_{18}N_2O_2S$ calculated = 349.0164, measured = 349.0159.

### 3.2.3.2. Reactivity of *2-(4-methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene :* Synthesis of *3-(p-methoxy-phenyl)-5-(methylthio)-1,2,4-oxadiazole.*




**347** **350 a**

**Scheme 3.51**

*2-(4-Methoxy-phenyl)-5-(methylthio)-7-phenyl-4-oxa-1,3-diaza-bicyclo[3.2.0]hept-2-ene* (80 mg, 0.24 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. After the completion of reaction in 18 hours, monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified with column chromatography (PE 40-60 $^oC$ / EtOAc : 8/1, Rf = 0.52). The product was obtained as an oily solid (45 mg, 88 %).

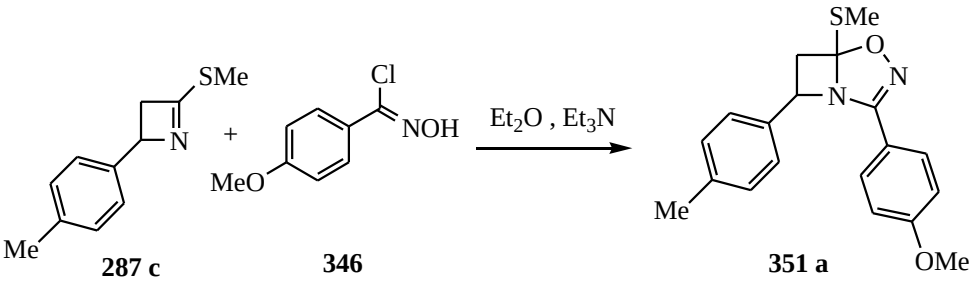
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2919 (m), 1611 (s), 1509 (s), 1466 (m), 1422 (m), 1346 (m), 1297 (m), 1250 (s), 1198 (m), 1117 (m), 1027 (m), 833 (s), 758 (s).

**$^1$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.99 (2H, d, *J*=8.0, ArH), 6.98 (2H, d, *J*=8.0, ArH), 3.85 (3H, s, OMe), 2.78 (3H, s, SMe).

**$^{13}$C NMR: $\delta_C$ (125 MHz, $CDCl_3$)** 178.05 (C, oxadiazole), 168.33 (C, oxadiazole), 161.99 (C, Ar), 129.09 (CH, Ar), 118.97 (C, Ar), 114.23 (CH, Ar), 55.38 (O-*C*$H_3$), 14.20 (S-*C*$H_3$).

**HRMS (*m/z*)** $[M+Na]^+$ for $C_{10}H_{10}N_2O_2S$ calculated = 245.0355, measured = 245.0350.

### 3.2.3.3. Synthesis of *2-(4-methoxy-phenyl)-5-(methylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**Scheme 3.52**

To a mixture of *2-methylthio-4-p-tolyl-1-azetine* (110 mg, 0.57 mmol) and 4-methoxybenzohydroximoylchloride (1 eq. 106 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 58 mg, 76.4 µl) diluted in dry diethyl ether (30 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.28) to give a yellow oil as product, 139 mg, 72 %.

**IR $\upsilon_{max}$ (cm$^{-1}$)** 2893 (w), 1608 (s) 1512 (s), 1346 (s), 1306 (m), 1255 (s), 1172 (s), 1051 (m), 1031 (m), 838 (m), 753 (m).

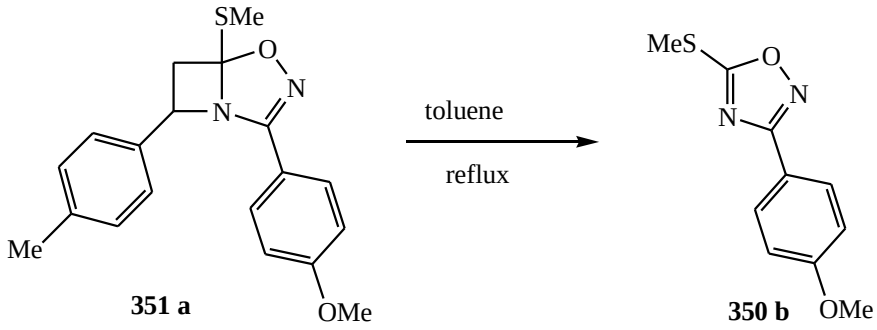
**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 7.42-7.39 (4H, m, 2 x $Ar^1$, 2 x $Ar^2$), 7.14 (2H, d, *J*=8.0 Hz, $Ar^1$), 6.71 (2H, d, *J*=7.2 Hz, $Ar^2$), 4.68 (1H, dd, *J*=5.3 and 9.3 Hz, $Ar^1CH$), 3.68 (3H, s, $OCH_3$), 3.54 (1H, dd, *J*=9.3 and 13.2 Hz, $Ar^1CHCH_2$), 2.61 (1H, dd, *J*= 13.2 and 5.3 Hz, $Ar^1CHCH_2$), 2.30 (3H, s, $SCH_3$), 2.13 (3H, s, $CH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 161.8 (N=C-N), 160.7 (C, Ar), 138.1 (C, Ar), 137.9 (C, Ar), 129.07 (CH, Ar), 128.7 (CH, Ar), 126.4 (CH, Ar), 116.9 (C, Ar), 114.7 (CH, Ar), 111.2 (*C*-SMe), 66.5 (CH), 55.4 ($OCH_3$), 44.7 ($CH_2$), 21.1 ($ArCH_3$), 10.4 ($SCH_3$).

**MS (*m/z*)** 341.1 [M+H$^+$], 363.1 [M+Na]$^+$.

**HRMS (*m/z*)** [M+H]$^+$ for $C_{19}H_{20}N_2O_2S$ calculated = 341.0501, measured = 341.0503.

**3.2.3.4. Reaction of *2-(4-methoxy-phenyl)-5-(methylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene :* Synthesis of *3-(p-methoxy-phenyl)-5-(methylthio)-1,2,4-oxadiazole.***




**351 a** **350 b**

**Scheme 3.53**

*2-(4-Methoxy-phenyl)-5-(methylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* (100 mg, 0.3 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. After the completion of reaction in 18 hours, monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified with column chromatography (PE 40-60 $^{o}$C / EtOAc : 8/1, Rf = 0.54). The product was obtained as an oily solid (52 mg, 82 %).

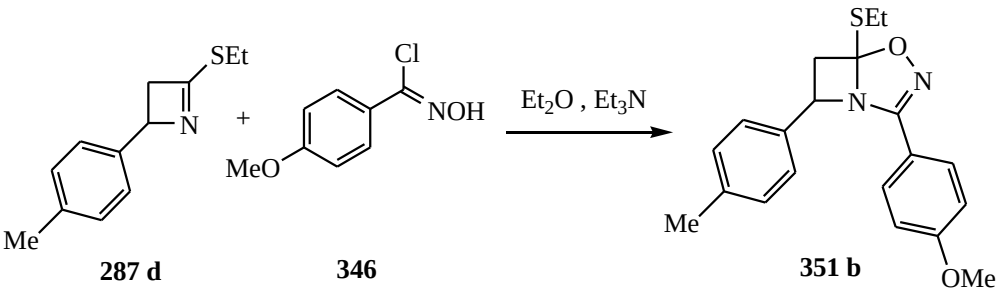
**IR $\upsilon_{max}$ (cm$^{-1}$)** 2919 (m), 1611 (s), 1509 (s), 1466 (m), 1422 (m), 1346 (m), 1297 (m), 1250 (s), 1198 (m), 1117 (m), 1027 (m), 833 (s), 758 (s).

**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.99 (2H, d, *J*=8.0, ArH), 6.98 (2H, d, *J*=8.0, ArH), 3.85 (3H, s, OMe), 2.78 (3H, s, SMe).

**$^{13}$C NMR: $\delta_C$ (125 MHz, $CDCl_3$)** 178.05 (C, oxadiazole), 168.33 (C, oxadiazole), 161.99 (C, Ar), 129.09 (CH, Ar), 118.97 (C, Ar), 114.23 (CH, Ar), 55.38 (O-*C*H$_3$), 14.20 (S-*C*H$_3$).

**HRMS (*m/z*)** $[M+Na]^+$ for $C_{10}H_{10}N_2O_2S$ calculated = 245.0355, measured = 245.0350.

### 3.2.3.5. Synthesis of *2-(4-methoxy-phenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**Scheme 3.54**

To a mixture of *2-ethylthio-4-p-tolyl-1-azetine* (100 mg, 0.48 mmol) and 4-methoxybenzohydroximoylchloride (1 eq. 92 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 50 mg, 70 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.30) to give a yellow oil as product, 80 mg, 48 %.

**IR $\upsilon_{max}$ (cm$^{-1}$)** 2915 (w), 1608 (s), 1590 (m), 1512 (s), 1345 (m), 1256 (s), 1173 (m), 1030 (m), 838 (m).

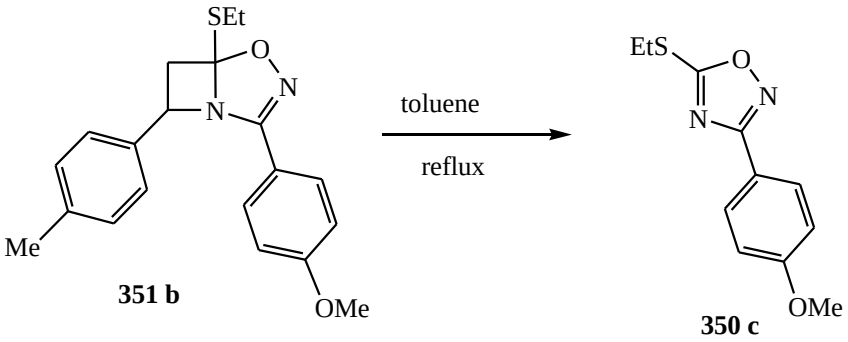
**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 7.54-7.49 (2H, m, ArH), 7.29-7.24 (2H, m, ArH), 6.95 (2H, dd, *J*=2.4 and 8.1 Hz, ArH), 6.83 (2H, d, *J*=7.2 Hz, ArH), 4.80 (1H, dd, *J*= 9.3 and 5.3 Hz, ArC*H*), 3.8 (3H, s, $OCH_3$), 3.62 (1H, dd, *J*= 13.2 and 9.3 Hz, ArCHC$H_2$), 2.92-2.75 (2H, m, SC$H_2$CH$_3$), 2.71 (1H, dd, *J*= 13.2 and 5.3 Hz, ArCHC$H_2$), 2.4 (3H, s, Ar-$CH_3$), 1.36 (3H, t, *J*=7.0, $SCH_2CH_3$).

**$^{13}$C NMR: δ (125 MHz, $CDCl_3$)** 161.8 (N=C-N), 160.7 (C, Ar), 138.0 (C, Ar), 137.8 (C, Ar), 129.4 (CH, Ar), 129.0 (CH, Ar), 126.4 (C, Ar), 114.4 (CH, Ar), 114.2 (CH, Ar), 111.5 (C, *C*SEt), 66.77 (CH), 55.3 ($OCH_3$), 45.4 (ArCH$CH_2$), 22.7 ($SCH_2$), 21.1 ($ArCH_3$), 14.8 ($SCH_2CH_3$).

**MS (*m/z*)** 377.1 $[M+Na]^+$, 731.2 $[M_2 + Na]^+$.

**HRMS (*m/z*)** $[M+H]^+$ for $C_{20}H_{22}N_2O_2S$ calculated = 355.0657, measured = 355.0657.

**3.2.3.6.** ***Reaction of 2-(4-methoxy-phenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene :*** **Synthesis of** ***3-(p-methoxy-phenyl)-5-(ethylthio)-1,2,4-oxadiazole.***




**351 b** **350 c**

**Scheme 3.55**

*2-(4-Methoxy-phenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* (80 mg, 0.22 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. After the completion of reaction in 18 hours, monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 8/1, Rf = 0.51). The product was obtained as an oily solid (41 mg, 81 %).

**IR $\upsilon_{max}$ (cm$^{-1}$)** 2920 (w), 1611 (s), 1505 (s), 1420 (m), 1348 (s), 1299 (m), 1250 (s), 1171 (m), 1028 (m), 838 (m), 753 (m).

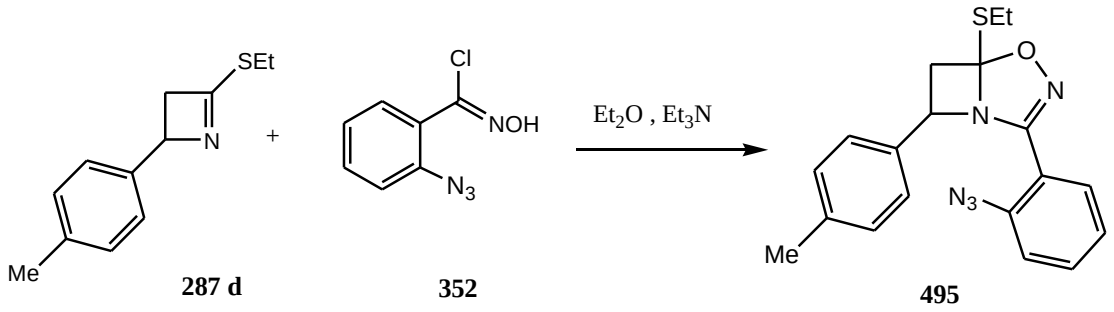
**$^{1}$H NMR: $\delta_H$ (500 MHz, $CDCl_3$):** 7.98 (2H, d, *J*=8.1 Hz, ArH), 6.96 (2H, d, *J*=8.1 Hz, ArH), 3.86 (3H, s, OMe), 3.32 (2H, q, *J*=7.9 Hz, C*H*$_2$CH$_3$), 1.52 (3H, t, *J*=7.9 Hz, CH$_2$C*H*$_3$).

**$^{13}$C NMR $\delta$ (125 MHz, $CDCl_3$):** 177.64 (C, oxadiazole), 168.27 (C, oxadiazole), 161.97 (C, Ar), 129.04 (CH, Ar), 119.04 (C, Ar), 114.22 (CH, Ar), 55.38 (O-*C*H$_3$), 27.25 (S-*C*H$_2$), 14.82 (S-CH$_2$*C*H$_3$).

**MS (*m/z*)** 259.0 [M+Na]$^+$, 731.2 [M$_2$ + Na]$^+$.

**HRMS (*m/z*)** [M+Na]$^+$ for $C_{11}H_{12}N_2O_2S$ calculated = 259.0511, measured = 259.0518.

### 3.2.3.7. Synthesis of *2-(2-azidophenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**Scheme 3.56**

To a mixture of *2-ethylthio-4-p-tolyl-1-azetine* (120 mg, 0.58 mmol) and 2-azidobenzohydroximoylchloride (1 eq. 114 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 58 mg, 81.3 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered off. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.36) to give an orange oil as product, 84 mg, 40 %.

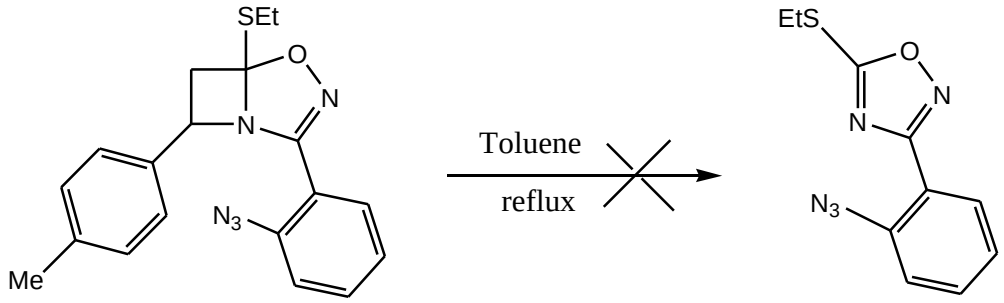
**IR $\upsilon_{max}$ (cm$^{-1}$)** 2914 (w), 2103 (m), 1604 (s), 1592 (m), 1512 (s), 1345 (m), 1253 (s), 1173 (m), 1031 (m), 838 (m).

**$^{1}$H NMR: δ (500 MHz, $CDCl_3$)** 8.15-8.17 (1H, m, ArH), 7.56-7.50 (2H, m, ArH), 7.46 (1H, d, *J*= 8.0 Hz), 7.39 (1H, d, *J*= 7.7 Hz, ArH), 7.30-7.21 (2H, m), 7.17 (1H, d, *J*= 6.2 Hz, ArH), 4.79 (1H, dd, *J*= 9.3 and 5.3 Hz, ArC*H*), 3.67 (1H, dd, *J*= 13.2 and 9.3 Hz, ArCHC$H_2$), 2.92-2.82 (2H, m, SC$H_2$CH$_3$), 2.72 (1H, dd, *J*=5.3 and 13.2 Hz, ArCHC$H_2$), 2.39 (3H, s, Ar-CH$_3$), 1.36 (3H, t, *J*=7.5, SCH$_2$C$H_3$).

**$^{13}$C NMR: δ (125 MHz, $CDCl_3$)** 155.1 (N=C-N), 139.3 (C, Ar), 138.5 (C, Ar), 132.2 (CH, Ar), 131.0 (CH, Ar), 130.8 (CH, Ar), 129.4 (C, Ar), 126.3 (C, Ar), 125.2 (CH, Ar), 118.8 (CH, Ar), 115.3 (CH, Ar), 111.08 (C, *C*SEt), 66.9 (CH), 45.5 (ArCH*C*H$_2$), 22.7 (S*C*H$_2$), 21.2 (ArCH$_3$), 14.2 (SCH$_2$*C*H$_3$).

**HRMS (*m/z*)** $[M+Na]^+$ 388.1202 for $C_{19}H_{19}N_5OSNa$, measured 388.1202.

### 3.2.3.8. Reaction of *2-(2-azidophenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*

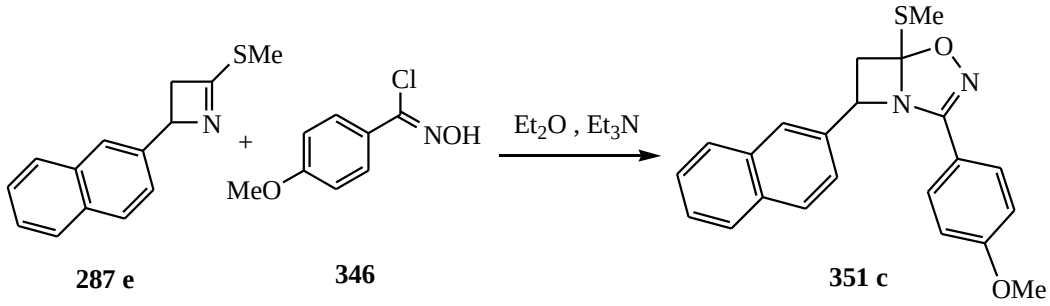



**495** **496**

**Scheme 3.57**

*2-(2-Azido-phenyl)-5-(ethylthio)-7-p-tolyl-4-oxa-1,3-diaza-bicyclo[3.2.0]hept-2-ene* (85 mg, 0.63 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. The reaction was monitored by TLC, no product could be identified due to the decomposition of starting material.

### 3.2.3.9. Synthesis of *2-(4-methoxyphenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**287 e** **346** **351 c**

**Scheme 3.58**

To a mixture of *2-methylthio-4-naphthyl-1-azetine* (100 mg, 0.43 mmol) and 4-methoxybenzohydroximoylchloride (1 eq. 81 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 44 mg, 61.5 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.37) to give an orange oil as product, 72 mg, 44 %.

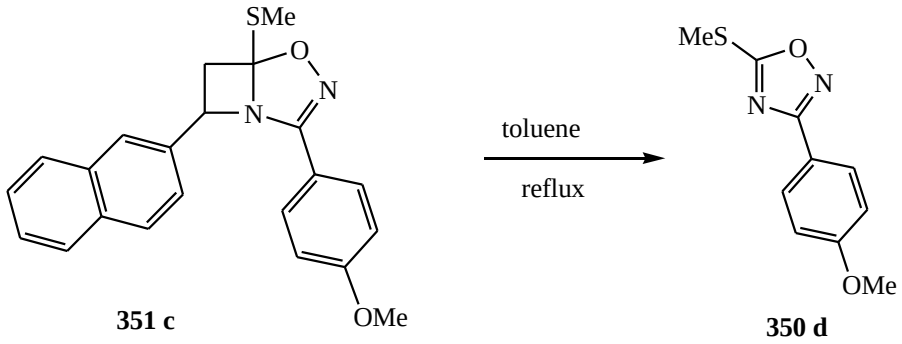
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2928 (w), 1608 (s), 1511 (s), 1404 (m), 1349 (m), 1256 (s), 1172 (m), 1028 (m), 836 (m).

**$^1$H NMR: δ (500 MHz, $CDCl_3$)** 7.98 (2H, d, *J*=8.8 Hz, 4-MeOAr), 7.94-7.85 (2H, m, naphth), 7.57-7.47 (3H, m, naphth), 7.0-6.95 (2H, m, naphth), 6.80 (2H, d, *J*=8.8 Hz, 4-MeOAr), 5.0 (1H, dd, *J*= 9.3 and 5.3 Hz, naphthC*H*), 3.77 (3H, s, $OCH_3$), 3.74 (1H, dd, *J*= 9.3 and 13.2 Hz, naphthCHC$H_2$), 2.82 (1H, dd, *J*= 13.2 and 5.3 Hz, naphthCHC$H_2$), 2.30 (3H, s, $SCH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 161.8 (N=C-N), 138.1 (C, Ar), 133.3 (C, Ar), 133.2 (C, Ar), 130.2 (C, Ar), 130.0 (CH, Ar), 129.0 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 126.8 (CH, Ar), 126.4 (CH, Ar), 125.2 (CH, Ar), 123.9 (CH, Ar), 116. 8 (CH, Ar), 114.4 (C, Ar), 111.3 (*C*-SMe), 66.6 (*C*H), 55.3 ($OCH_3$), 44.7 ($CH_2$), 10.4 ($SCH_3$).

**HRMS (*m/z*)** $[M + Na]^+$ for $C_{22}H_{20}N_2O_2S$ calculated 399.1138 measured 399.1142.

### 3.2.3.10. Reaction of *2-(4-methoxyphenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* : synthesis of *3-methoxyphenyl-5-methylthio-1,2,4-oxadiazole.*




**351 c** **350 d**

**Scheme 3.59**

*2-(4-Methoxyphenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* (70 mg, 0.19 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. After the completion of reaction in 20 hours, monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 8/1, Rf = 0.53). The product was obtained as an oily solid (34 mg, 87 %).

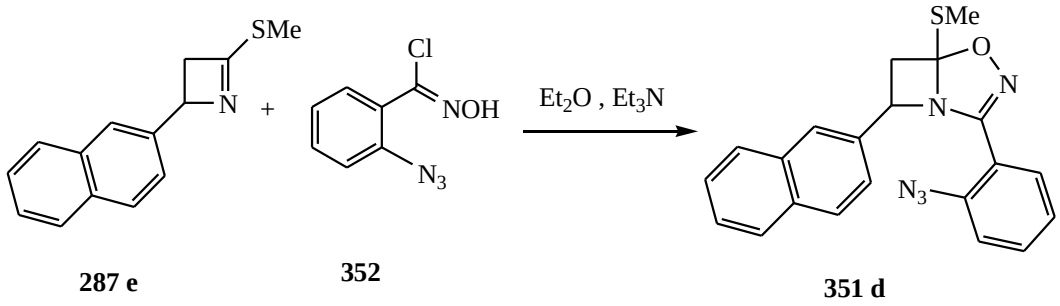
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2919 (m), 1611 (s), 1509 (s), 1466 (m), 1422 (m), 1346 (m), 1297 (m), 1250 (s), 1198 (m), 1117 (m), 1027 (m), 833 (s), 758 (s).

**$^1$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.99 (2H, d, *J*=8.0, ArH), 6.98 (2H, d, *J*=8.0, ArH), 3.85 (3H, s, OMe), 2.78 (3H, s, SMe).

**$^{13}$C NMR: $\delta_C$ (125 MHz, $CDCl_3$)** 178.05 (C, oxadiazole), 168.33 (C, oxadiazole), 161.99 (C, Ar), 129.09 (CH, Ar), 118.97 (C, Ar), 114.23 (CH, Ar), 55.38 (O-*C*$H_3$), 14.20 (S-*C*$H_3$).

**HRMS (*m/z*)** $[M+Na]^+$ for $C_{10}H_{10}N_2O_2S$ calculated = 245.0355, measured = 245.0350.

### 3.2.3.11. Reaction of *2-methylthio-4-naphthyl-1-azetine with 2-azidobenzohydroximoyl chloride* : Synthesis of *2-(2-azidophenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**287 e** **352** **351 d**

**Scheme 3.60**

To a mixture of *2-methylthio-4-naphthyl-1-azetine* (100 mg, 0.43 mmol) and 2-azidobenzohydroximoylchloride (1 eq. 86.06 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 44 mg, 61.5 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent in *vacuo* the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 5/1, Rf = 0.39) to give an orange oil as product, 74 mg, 44 %.

**IR $\upsilon_{max}$ ($cm^{-1}$)** 2968 (m), 2918 (m), 2128 (s), 1597 (m), 1581 (m), 1447 (m), 1300 (m), 751 (m).

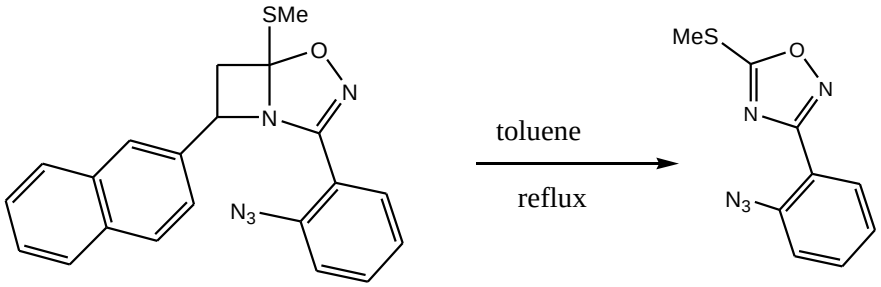
**$^1$H NMR: $\delta$ (500 MHz, $CDCl_3$)** 7.95-7.85 (2H, m, Ar), 7.82 (1H, dd, *J*=7.0 and 1.5 Hz, Ar), 7.58-7.50 (2H, m, Ar), 7.44-7.38 (2H, m, Ar), 7.28-7.23 (2H, m, Ar), 7.18 (1H, d, *J*=8.0 Hz, Ar), 6.96 (1H, td, *J*=1.0 and 7.0 Hz, Ar), 5.0 (1H, dd, *J*= 9.3 and 5.3 Hz, Ar*CH*N), 3.7 (1H,

dd, *J*= 13.2 and 9.3 Hz, ArCH*CH*$_2$), 2.8 (1H, dd, *J*= 5.3 and 13.2 Hz, ArCH*CH*$_2$) 2.3 (3H, s, $SCH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 158.8 (N=C-N), 139.1 (C, Ar), 137.9, (C, Ar), 133.2 (C, Ar), 132.2 (C, Ar), 132.0 (CH, Ar), 131.0 (CH, Ar), 130.2 (CH, Ar), 128.9 (CH, Ar), 128.4 (CH, Ar), 128.0 (CH, Ar), 126.4 (CH, Ar), 126.3 (CH, Ar), 124.8 (CH, Ar), 124.0 (CH, Ar), 119.6 (CH, Ar), 118.8 (C, Ar), 116.1 (*C*-SMe), 66.8 (*CH*), 22.7 (*CH*$_2$), 10.8 (*CH*$_3$).

**HRMS (*m/z*)** $[M + Na]^+$ for $C_{21}H_{17}N_5OS$ calculated 410.1046, measured 410.1046.

### 3.2.3.12. Reaction of *2-(2-azidophenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* : Synthesis of *3-azidophenyl-5-methylthio-1,2,4-oxadiazole.*




**351 d** **350 e**

**Scheme 3.61**

*2-(2-Azidophenyl)-5-(methylthio)-7-naphthyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* (100 mg, 0.25 mmol) was added to toluene (10 ml) and the mixture was heated at reflux overnight. After the completion of reaction (24h), monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 8/1, Rf = 0.51). The product was obtained as an oily solid (41 mg, 68 %).

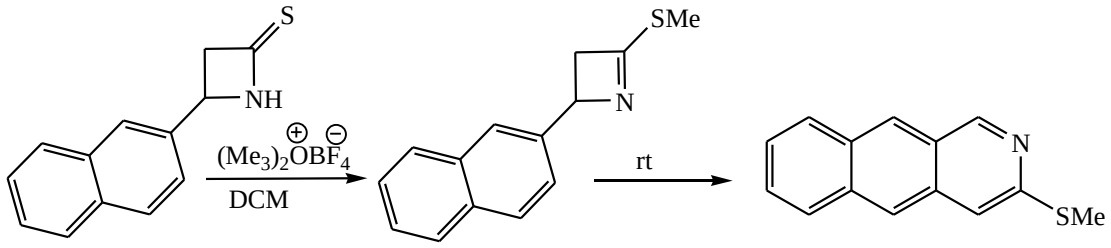
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2966 (w), 2128 (s), 1597 (m), 1578 (m), 1501 (m), 1300 (m), 750 (m).

**$^1$H NMR: $\delta_H$ (500 MHz, $CDCl_3$)** 7.97 (1H, dd, *J*=2.0 and 8.0 Hz, ArH), 7.55-7.45 (1H, m, ArH), 7.37 (1H, dd, *J*=2.0 and 8.0 Hz, ArH), 7.27-7.22 (1H, m, ArH), 2.7 (3H, s, $SCH_3$).

**$^{13}$C NMR δ (125 MHz, $CDCl_3$)** 178.0 (C, oxadiazole), 166.7 (C, oxadiazole), 138.8 (C, Ar), 132.1 (CH, Ar), 131.0 (CH, Ar), 124.9 (CH, Ar), 119.3 (CH, Ar), 118.9 (C, Ar), 15.3 (S*C*H$_3$).

**HRMS (*m/z*)** $[M+Na]^+$ for $C_9H_7N_5OS$ calculated 256.0264 measured 256.0273.

### 3.2.3.13 Reactivity of *2-methylthio-4-naphthyl-1-azetine* ; Synthesis of 2-methylthio-benzoquinoline.




**286 c** **289** **293**

**Scheme 3.62**

To *4-naphthylazetidin-2-thione* (300 mg, 1.40 mmol) was added Meerwein's reagent (312.5 mg, 2.11 mmol, 1.5 eq.) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was then added drop wise to a 50% aqueous solution of potassium carbonate (10 ml) at -10 $^oC$. The solution was then filtered through celite and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 ml), and the combined organic extracts were dried over magnesium sulfate. After filtration the solvent was evaporated *in vacuo* to give a dark orange oil which was kept at room temperature for 24 hour to give the product **294** as a yellow solid (112 mg, 35 %).

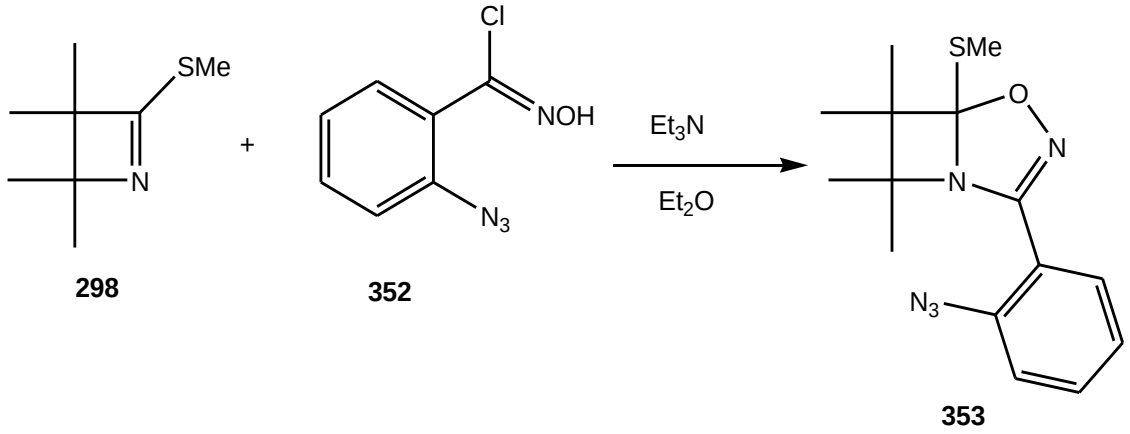
**IR $\upsilon_{max}$ ($cm^{-1}$):** 3043 (w), 2955 (m), 1704 (m), 1587 (w), 1556 (w), 1493 (m), 1441 (m), 1391 (m), 1144 (s), 1224 (m), 1073 (m), 835 (m), 748 (m).

**$^1$H NMR: δ (400 MHz, $CDCl_3$):** 9.27 (1H, d, *J* = 7.6 Hz), 7.88 (2H, t, 3 *J* = 9.7 Hz), 7.71-7.58 (4H, m), 7.36 (1H, d, *J* = 8.4 Hz), 2.83 (3H, s, SMe).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 158.51 (C), 146.18 (C), 135.31 (CH), 133.90 (C), 130.91 (C), 128.02 (CH), 127.72 (CH), 126.67 (CH), 126.55 (CH), 125.46 (CH), 124.41 (CH), 123.22 (C), 120.87 (CH), 13.26 (SMe).

**HRMS (*m/z*)** $[M+H]^+$ for $C_{14}H_{12}N_1S$ calculated 226.0692, measured 226.0684.

### 3.2.3.14. Reaction of 2-methylthio-3,3,4,4-tetramethyl-1-azetine with 2-azidobenzohydroximoyl chloride : Synthesis of *2-(2-azidophenyl)-5-(methylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene.*




**Scheme 3.63**

To a mixture of 2-methylthio-3,3,4,4-tetramethyl-1-azetine (250 mg, 1.57 mmol) and 2-azidobenzohydroxyimoylchloride (1 eq. 308 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 159 mg, 218.8 µl) diluted in dry diethyl ether (30 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and precipitates were filtered. After removing the solvent *in vacuo* the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 10/1, Rf = 0.31) to give a yellow oil as product, 262 mg, 52 %.

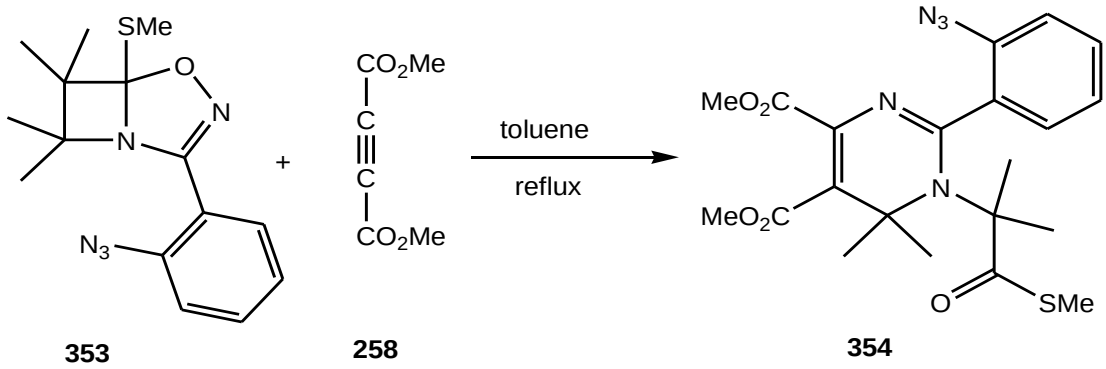
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2959, 2925, 2127 and 2093 ($N_3$), 1581 (CN), 1481, 1447, 1397.

**$^1$H NMR (400 MHz) ($CDCl_3$)** δ 7.66 (1H, d, *J*= 7.8 Hz, ArH), 7.56-7.43 (1H, m, ArH), 7.25 (1H, d, *J*= 8.2 Hz, ArH), 7.22-7.14 (1H, m, ArH), 2.1 (3H, s, $SCH_3$), 1.50 (3H, s, $CH_3$), 1.32 (3H, s, $CH_3$), 1.26 (3H, $CH_3$), 0.97 (3H, s, $CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$)** δ 157.36 (CN), 138.36 (C), 131.54 (CH), 130.77 (CH), 124.68 (CH), 119.83 (CH), 118.80 (C), 117.14 (C), 71.85 (C), 52.75 (C), 26.65 ($CH_3$), 21.09 ($CH_3$), 20.52 ($CH_3$), 20.13 ($CH_3$), 9.69 ($SCH_3$).

**MS. (ESI, m/z)**, 340.1203 $(M+Na)^+$ calculated for $C_{15}H_{19}N_5OSNa$ and found 340.1200.

### 3.2.3.15. Reaction of *2-(2-azidophenyl)-5-(methylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* with DMAD : Synthesis of *dimethyl 2-(2-azidophenyl)-6,6-dimethyl-1-(2-methyl-3-oxobutan-2-yl)-1,6-dihydropyrimidine-4,5-dicarboxylate*.




**353** **258** **354**

**Scheme 3.64**

To a solution of *2-(2-azidophenyl)-5-(methylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene* (130 mg, 0.41 mmol) in dry toluene (10 ml) was added DMAD (1 eq. 58 mg, 50.3 µl) and the mixture was heated at reflux overnight in a nitrogen atmosphere. After the completion of reaction in 18 hours, monitored by TLC, the solvent was evaporated *in vacuo* and the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 4/1, Rf = 0.35). The product was obtained as an oily solid (68 mg, 36 %).

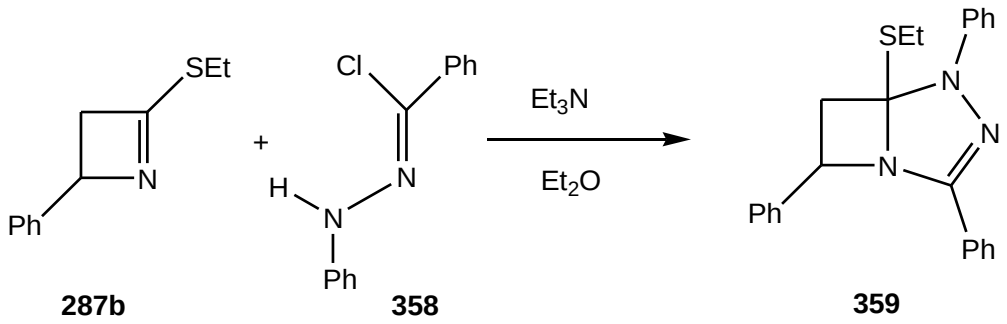
**IR $\upsilon_{max}$ ($cm^{-1}$)** 2953 (w), 2928 (w), 2129 ($N_3$), 1732 (s, C=O), 1665 (m, C=N), 1556 (m), 1444 (m), 1361 (m), 1289(m), 1230 (m), 1203 (m), 1173 (m), 1127 (m), 1078 (m).1003 (m), 825 (m), 765 (m).

**$^1$H NMR δ (400 MHz, $CDCl_3$)** 8.26 (1H, d, *J*=7.5 Hz, CH (Ar)), 7.71 (1H, m, CH (Ar)), 7.56 (1H, d, *J*=7.2 Hz, CH (Ar)), 7.27 (1H, m, CH (Ar)), 4.01 (3H, s, $CO_2Me$), 3.74 (3H, s, $CO_2Me$), 2.25 (3H, s, $SCH_3$), 1.46 (6H, s, 2 x Me), 1.31 (6H, s, 2 x Me).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$)** 204.66 (O=C-SMe), 165.18 (NC=N), 160.43 (C=O), 158.20 (C=O) 136.40 (C (Ar)), 133.07 (C=C), 131.96 (C=C), 131.52 (CH, Ar), 130.12 (C, Ar), 128.66 (CH, Ar), 127.27 (CH, Ar), 124.59 (C-Ar), 64.77 ($C(CH_3)_2$), 55.51 $C(CH_3)_2$), 53.30 ($CO_2CH_3$), 52.71 ($CO_2CH_3$) 26.99 ($CH_3$), 25.44 $(CH_3)_2$, 21.78 ($CH_3$), 19.59 $(CH_3)_2$, 12.08 ($SCH_3$).

**HRMS (*m/z*)** $[M+Na]^+$ for $C_{21}H_{25}N_5O_5SNa$ calculated 482.1468, measured 482.1472.

### 3.2.3.16. Reaction of 2-ethylthio-4-phenyl-1-azetine with α-chlorobenzaldehyde phenylhydrazine : Synthesis of *2,4,7-triphenyl-5-(ethylthio)-1,3,4-triazabicyclo[3.2.0]hept-2-ene.*




**287b** **358** **359**

**Scheme 3.65**

To a mixture of 2-ethylthio-4-phenyl-1-azetine (200 mg, 1.05 mmol) and α-chlorobenzaldehyde phenylhydrazine (1 eq. 241 mg) in dry diethyl ether (5 ml) was added triethylamine (1.1 eq. 116 mg, 165 µl) diluted in dry diethyl ether (30 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and then heated at reflux for 3 h. After filtering and removing the solvent *in vacuo* the mixture was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 8/1, Rf = 0.31) to give a yellow oily solid as the product, 82 mg, 20 %.

**$^1$H NMR δ (400 MHz) ($CDCl_3$)** 8.20 (2H, dd, *J*= 6.9 and 1.3 Hz, ArH), 7.52-7.46 (6H, m, ArH), 7.25-7.20 (7H, m, ArH), 4.54 (1H, dd, *J*= 9.3 and 5.3 Hz, Ph-C*H*), 3.45-3.27 (2H, m, $CH_2$-ring), 2.33 (2H, 2x dq, *J*= 7.3 and 3.8 Hz, $SCH_2$), 1.15 (3H, t, *J*= 7.3 Hz, $CH_3$).

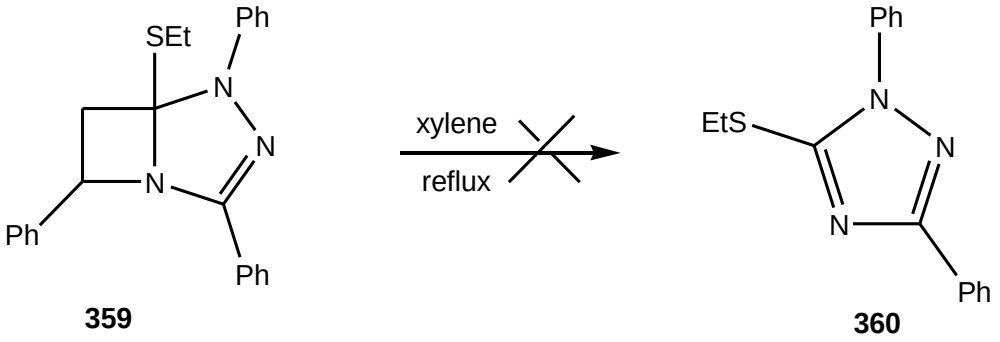
**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 161.58 (CN), 154.31 (C), 141.06 (C), 137.08 (C), 130.90 (C), 129.39 (CH), 129.30 (CH), 129.16 (CH), 128.59 (CH), 128.56 (CH), 127.69 (CH),

127.46 (CH), 126.50 (CH), 125.85 (CH), 48.01 (CH), 33.85 ($CH_2$), 25.54 ($CH_2$), 14.39 ($CH_3$).

**MS. (ESI, *m/z*),** 408.15 $(M+Na)^+$.

**HRMS (m/z):** 408.1505 calculated for $C_{23}H_{25}NNaOS$, $(M+Na)^+$, found 408.1517

### 3.2.3.17. Reactivity of *2,4,7-triphenyl-5-(ethylthio)-1,3,4-triazabicyclo[3.2.0]hept-2-ene* : Attempted synthesis of 2,4-diphenyl-5-ethylthio-1,3,4-triazole.



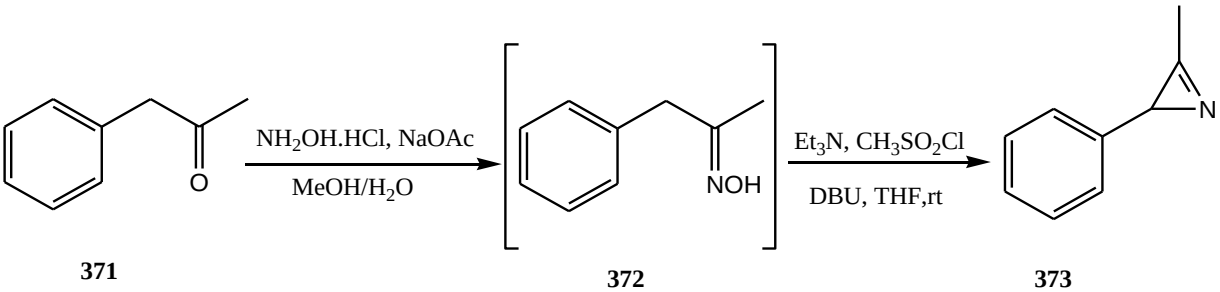

**359** **360**

**Scheme 3.66**

5-Ethylthio-2,4,7-triphenyl-1,3,4-triazabicyclo[3.2.0]hept-2-en-4-one (100 mg, 0.26 mmol) was added to *o*-xylene (8 ml) and the mixture was heated at reflux at 155 $^oC$ overnight. The reaction was monitored on TLC and even after 72 hours of reflux no product could be identified.

## 3.3 Synthesis and reactivity of 1-azirines

### 3.3.1. Synthesis of 2-methyl-3-phenyl-1-azirine[254].




**371** **372** **373**

**Scheme 3.67**

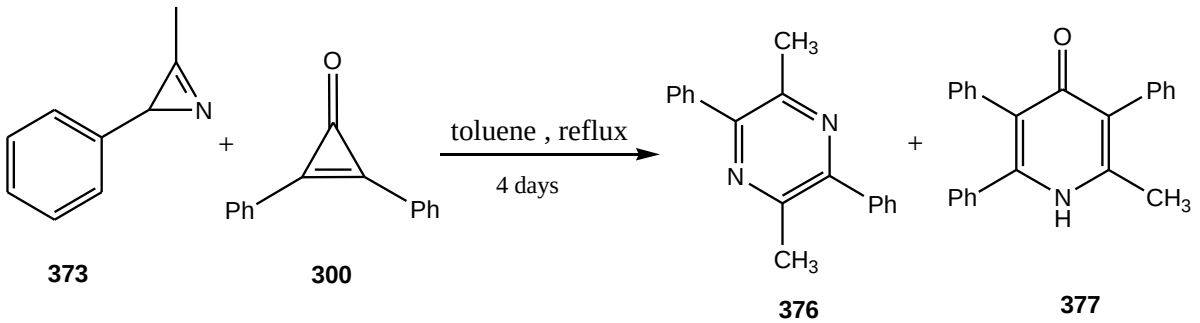
To a mixture of phenyl acetone (1 g, 1 ml, 7.46 mmol) in MeOH (20 ml) and water (1 ml) was added hydroxylamine hydrochloride (1.5 eq. 778.5 mg) and sodium acetate (1.5 eq. 918.4 mg) in a round bottom flask. After stirring the mixture for 4 h at room temperature, the solvent was removed *in vacuo*. The reaction mixture was dissolved in EtOAc and washed with water, saturated aqueous $NaHCO_3$ solution and brine and dried over $MgSO_4$. Distillation of the solvent resulted in the crude oxime (1.48 g) which was used directly in the next reaction.

To a stirring mixture of crude oxime (1.48 g) in dry THF (30 ml) was added $Et_3N$ (11.2 mmol, 1.13 g, 2.08 ml) and methanesulfonyl chloride (11.2 mmol, 1.28 g, 0.86 ml) sequentially at room temperature. The solution turned cloudy after the addition of methanesulfonyl chloride. After 30 min. of stirring, DBU (22.4 mmol, 3.4 g, 3.34 ml) was added over 1 min. and the mixture was stirred for a further 30 min. Then reaction mixture was passed through a pad of silica gel, and washed with EtOAc. After removing the solvent *in vacuo* the mixture was chromatographed (PE / EtOAc : 10/1, Rf = 0.68) to give the product as a colourless oil, 536 mg, 55 % from ketone[271].

**$^1$H NMR δ (400 MHz) ($CDCl_3$)** 7.30-7.18 (3H, m), 7.04 (2H, d, *J*= 8.2 Hz), 2.85 (1H, s, CH), 2.46 (3H, s, $CH_3$).

**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 164.44 (CN), 141.31 (C), 128.85 (CH), 127.24 (CH), 125.65 (CH), 33.39 (CH), 12.85 ($CH_3$).

### 3.3.2. Reactivity of 2-methyl-3-phenyl-1-azirine with diphenylcyclopropenone : Synthesis of 2,5-dimethyl-3,6-diphenylpyrazine and 2-methyl-3,5,6-triphenylpyridine-4-(1*H*)-one [255].




**373** **300** **376** **377**

**Scheme 3.68**

To a solution of the azirine (160 mg, 1.22 mmol) in dry toluene (10 ml) was added diphenylcyclopropenone (1 eq. 252 mg) and the mixture was heated at reflux for 4 days. After completion of the reaction, the mixture was purified with flash chromatography (PE / EtOAc : 10/1, Rf = 0.42) to give the pyrazine (61 mg, 19 %) as a yellow solid, m.p. 157-161 $^{o}$C and the pyridone (Rf = 0.24) as a yellow solid (21 mg, 5 %), m.p. 250.5-253 $^{o}$C.

**Pyrazine**

**IR $\upsilon_{max}$ (cm$^{-1}$)** 2907 (w), 1627(s), 1600 (s), 1507 (m), 1347 (s), 694 (m).

**$^{1}$H NMR δ (400 MHz) ($CDCl_3$)** 7.63 (4H, d, *J*= 7.1 Hz, ArH), 7.42-7.51 (6H, m, ArH), 2.64 (6H, s, 2x$CH_3$).

**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 151.08 (C), 147.84 (C), 138.80 (C), 128.92 (CH), 128.35 (CH), 128.24 (CH), 22.69 (2xCH3).

**HRMS (m/z):** 261.1386 calculated for $C_{18}H_{17}N_2$, $(M+H)^+$, found 261.1388.

**Pyridone**

**IR $\upsilon_{max}$ (cm$^{-1}$)** 3400, 1687, 1600, 1493, 1447.

**$^{1}$H NMR δ (400 MHz) ($CDCl_3$)** 8.1 (2H, d, *J*= 7.5 Hz, ArH), 7.95 (1H, s, NH), 7.88 (2H, t, *J*= 8.1 Hz, ArH), 7.61-7.22 (7H, m, ArH), 7.14 (2H, t, *J*= 7.7 Hz, ArH), 7.06 (2H, d, *J*= 7.5 Hz, ArH), 2.63 (3H, s, $CH_3$).

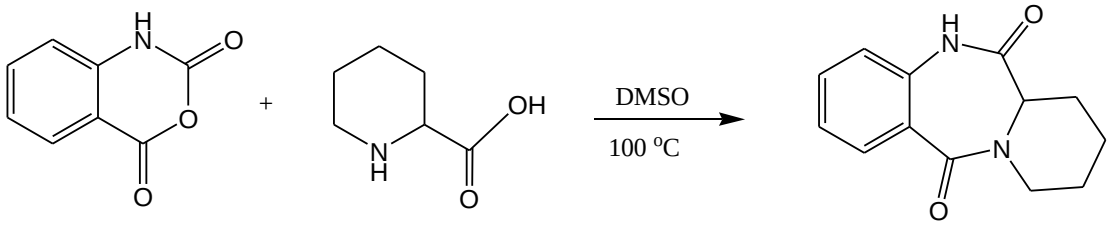
**$^{13}$C NMR δ (100 MHz) ($CDCl_3$)** 172.64 (C=O), 166.97 (C), 165.88 (C), 148.10 (C), 142.25 (CH), 135.45 (C), 134.36 (C), 133.65 (C), 131.62 (CH), 130.85 (CH), 130.18 (CH), 129.74 (CH), 128.75 (CH), 128.46 (CH), 128.28 (CH), 126.30 (CH), 123.91 (C), 25.66 ($CH_3$).

The data is identical to literature[272].

## 3.4. Synthesis and reactivity of benzodiazepines

## 3.4.1. Synthesis of benzodiazepines

### 3.4.1.1. Synthesis of 1,2,3,11a-tetrahydro-10H-picolo[2,1-c][1,4]benzodiazepine-5,11-dione [280].




**395** **497** **397 a**

**Scheme 3.69**

Isatoic anhydride (4.1 g, 25 mmol) and pipecolic acid (1.61g, 1 eq.) were heated in DMSO (15 ml) for 5 h at 100 $^{o}$C. The reaction mixture was cooled and added to iced water (150 ml), the precipitate was isolated and recrystallized from ethanol to give the product as light brown crystals 3.8 g, 66%.

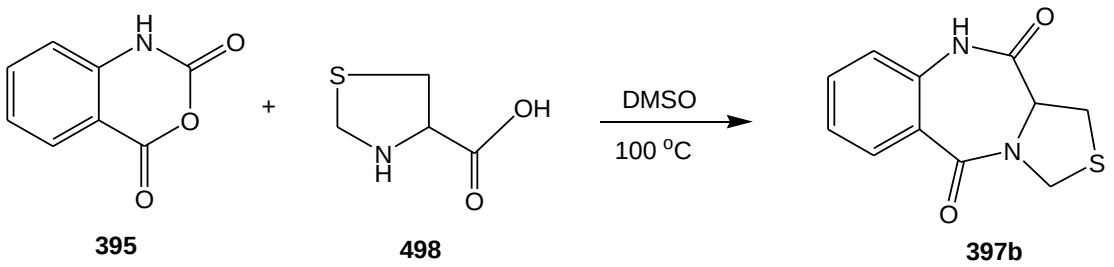
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3246 (NH), 1697, 1636 $cm^{-1}$ (2x C=O)

**$^{1}$H NMR δ (500 MHz) (DMSO-$d_6$)** 10.4 (1H, s, NH), 7.78 (1H, dd, *J*= 7.9 and 1.5 Hz, ArH), 7.55 (1H, dt, *J*= 8.1 and 1.2 Hz, ArH), 7.33 (1H, dt, *J*= 8.0 and 1.2 Hz, ArH), 7.24 (1H, d, *J*= 8.0 Hz, ArH), 4.41 (1H, dd, *J*= 13.2, 3.1 Hz, CH), 4.26 (1H, dd, *J*= 6.7, 3.5 Hz, $CH_2$), 2.71-2.84 (1H, m, $CH_2$), 2.35-2.15 (2H, m, $CH_2$), 1.8-1.4 (4H, m, 2 x $CH_2$).

**$^{13}$C NMR δ (125 MHz)** 171.5 (C=O), 168.15 (C=O), 137.37 (Ar), 132.33 (Ar), 130.93 (Ar), 127.5 (Ar), 124.3 (Ar), 120.9 (Ar), 50.9 (CH), 39.05 ($CH_2$), 25.28 ($CH_2$), 23.30 ($CH_2$), 19.3 ($CH_2$).

Data as reported[280].

**3.4.1.2. Synthesis of 1,2,3,10,11,11a(S)-Hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-5,11-dione [280].**




**395** **498** **397b**

**Scheme 3.70**

Isatoic anhydride (1.2 g, 7.36 mmol) and thiazoline-4-carboxylic acid (981 mg, 1 eq.) were heated in DMSO (10 ml) for 5 h at 100 °C. The reaction mixture was cooled and added to iced water (75 ml) which was extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with water many times to remove the DMSO. After the mixture was dried with magnesium sulfate and evaporated, the product was obtained as yellow solid which was recrystallized from ethyl acetate and petroleum ether 60-80 °C to yield a cream crystalline solid 1.62 g, 94%.

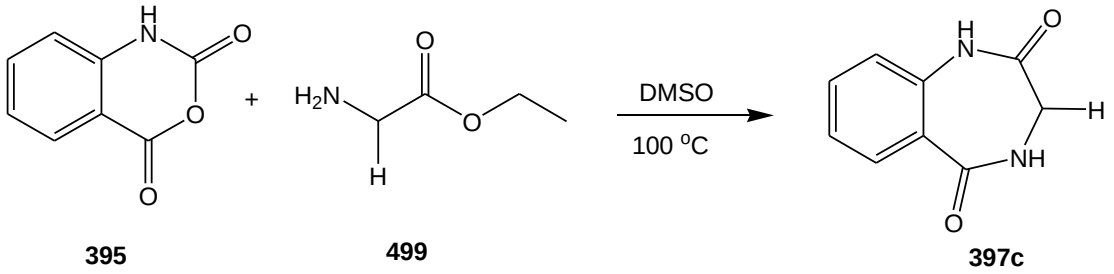
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3430 (NH) 1701, 1636 $cm^{-1}$ (2x C=O)

**$^{1}$H NMR δ (400 MHz) (DMSO-$d_6$)** 8.58 (1H, s, NH), 8.02 (1H, d, *J*= 8.1 Hz, ArH), 7.52 (1H, t, *J*= 7.4 Hz, ArH), 7.27 (1H, t, *J*= 7.4 Hz, ArH), 7.02 (1H, d, *J*= 8.2 Hz, ArH), 4.88 (1H, d, *J*= 10.4 Hz, C*H*N), 4.74 (1H, d, *J*= 10.4 Hz, C*H*N), 4.32 (1H, dd, *J*= 3.3 and 6.8 Hz, C*H*CO), 3.85 (1H, dd, *J*= 3.3 and 12.3 Hz, C*H*S), 3.23 (1H, dd, *J*= 6.8 and 12.3 Hz, C*H*S).

**$^{13}$C NMR δ (100 MHz) (DMSO-$d_6$)** 169.99 (C=O), 164.96 (C=O), 135.28 (Ar), 133.24 (Ar), 131.67 (Ar), 126.49 (Ar), 125.53 (Ar), 121.28 (Ar), 58.62 (CH), 50.54 ($CH_2$), 31.58 ($CH_2$).

Data as reported[280].

### 3.4.1.3. Synthesis of 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione [280].




**395** **499** **397c**

**Scheme 3.71**

Isatoic anhydride (2 g, 0.012 mol) and the glycine ethyl ester HCl (1.71g, 1 eq.) in anhydrous pyridine (10 ml) were heated at reflux for 16 h. The cooled reaction mixture was poured on to iced water (200 ml) and the precipitate collected as a cream powder (1.67 g, 79%).

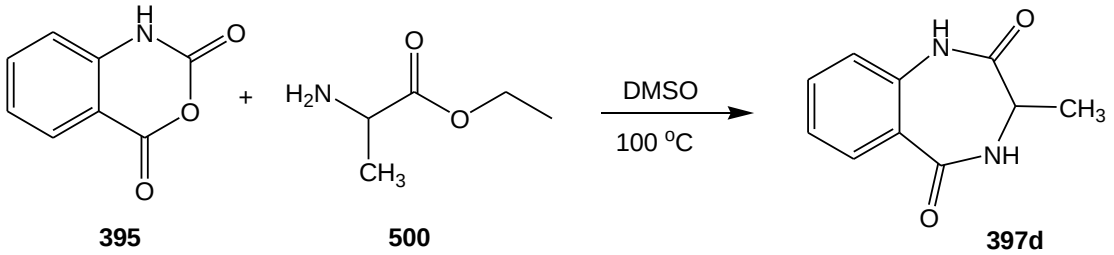
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3178 (NH) 1701, 1670 $cm^{-1}$ (2x C=O)

**$^1$H NMR δ (400 MHz) (DMSO-$d_6$)** 10.37 (1H, s, NH), 8.55 (1H, t, *J*= 5.8 Hz, NH), 7.74 (1H, dd, *J*= 7.7 and 1.6 Hz, ArH), 7.52 (1H, dt, *J*= 7.2 and 1.6 Hz, ArH), 7.22 (1H, dt, *J*= 7.7 and 1.2 Hz, ArH), 7.11 (1H, dd, *J*= 8.2 and 0.9 Hz, ArH), 3.56 (2H, d, *J*= 5.8 Hz, C*HH*).

**$^{13}$C NMR δ (100 MHz) (DMSO-$d_6$)** 171.61 (C=O), 168.54 (C=O), 137.61 (Ar), 132.72 (Ar), 131.27 (Ar), 125.98 (Ar), 124.35 (Ar), 121.37 (Ar), 44.92 (CH2).

Data as reported[280].

### 3.4.1.4. Synthesis of 3-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione [280].




**395** **500** **397d**

**Scheme 3.72**

Isatoic anhydride (2 g, 0.012 mol) and L-alanine methyl ester HCl (1.67g, 1 eq.) in anhydrous pyridine (10 ml) were heated at reflux for 16 h. The cooled reaction mixture was poured on to iced water (200 ml) and the precipitate collected as white powder (130 mg, 6%).

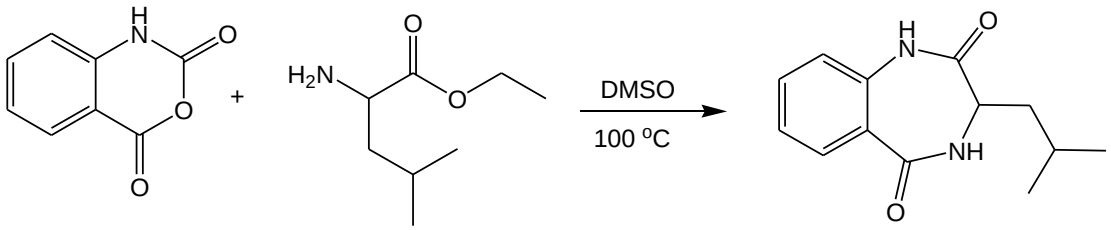
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3169 (NH) 1705, 1675 $cm^{-1}$ (2x C=O)

**$^1$H NMR δ (400 MHz) (DMSO-$d_6$)** 10.37 (1H, s, NH), 8.4 (1H, d, *J*= 5.1 Hz, NH), 7.74 (1H, d, *J*= 7.8 Hz, ArH), 7.52 (1H, dt, *J*= 7.4 and 1.6 Hz, ArH), 7.22 (1H, t, *J*= 7.7 Hz, ArH), 7.09 (1H, d, *J*= 7.8 Hz, ArH), 3.82-3.76 (1H, m, C*H*CO), 1.23 (3H, d, *J*= 6.7 Hz, $CH_3$).

**$^{13}$C NMR δ (100 MHz) (DMSO-$d_6$)** 167.96 (C=O), 162.78 (C=O), 135.86 (Ar), 133.21 (Ar), 131.85 (Ar), 126.46 (Ar), 124.33 (Ar), 121.23 (Ar), 52.51 (CH), 14.26 ($CH_3$).

Data as reported[280].

### 3.4.1.5. Synthesis of 3-isobutyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione [280].




**395** **501** **397e**

**Scheme 3.73**

Isatoic anhydride (2 g, 0.012 mol) and L-leucine methyl ester HCl (2.18 g, 1 eq.) in anhydrous pyridine (10 ml) were heated at reflux for 16 h. The cooled reaction mixture was poured on to iced water (200 ml) and the precipitate collected as white powder (1.83 g, 66%).

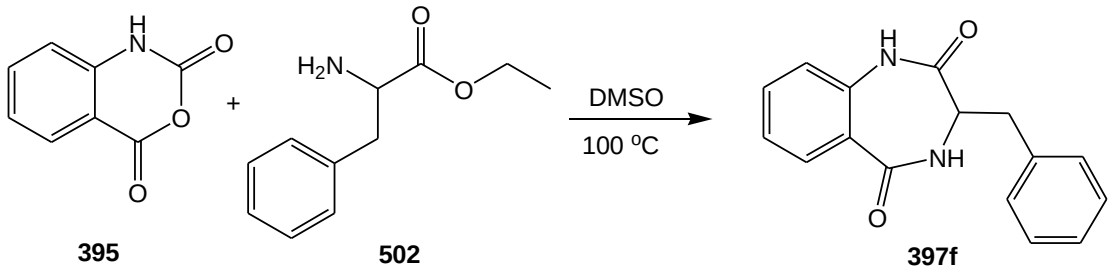
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3166 (NH) 1681, 1664 $cm^{-1}$ (2x C=O)

**$^1$H NMR δ (400 MHz) (DMSO-$d_6$)** 10.38 (1H, s, NH), 8.45 (1H, d, *J*= 5.8 Hz, NH), 7.74 (1H, dd, *J*= 7.9 and 1.5 Hz, ArH), 7.50 (1H, dt, *J*= 8.6 and 1.5 Hz, ArH), 7.19 (1H, t, *J*= 6.9 Hz, ArH), 7.10 (1H, d, *J*= 7.9 Hz, ArH), 3.63-3.56 (1H, m, C*H*CO), 1.75-1.69 (1H, m, CH), 1.56 (2H, t, *J*= 7.1 Hz, $CH_2$), 0.84 (3H, d, *J*= 6.6 Hz, $CH_3$), 0.76 (3H, d, *J*= 6.6 Hz, $CH_3$).

**$^{13}$C NMR δ (100 MHz) (DMSO-$d_6$)** 172.12 (C=O), 168.22 (C=O), 137.20 (Ar), 132.68 (Ar), 130.83 (Ar), 127.62 (Ar), 124.37 (Ar), 121.35 (Ar), 50.67 (CH), 36.60 (CH), 24.32 ($CH_2$), 23.29 and 21.99 (2 x $CH_3$).

Data as reported[280].

### 3.4.1.6. Synthesis of 3-benzyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione [280].




**395** **502** **397f**

**Scheme 3.74**

Isatoic anhydride (2 g, 0.012 mol) and L-phenylalanine ethyl ester HCl (2.75 g, 1 eq.) in anhydrous pyridine (10 ml) were heated at reflux for 16 h. The cooled reaction mixture was poured on to iced water (200 ml) and the precipitate collected as a cream powder (1.81 g, 57%).

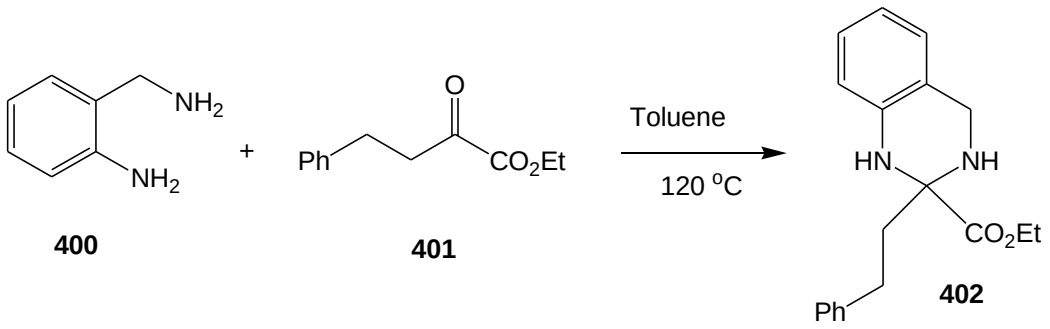
**IR $\upsilon_{max}$ ($cm^{-1}$)** 3169 (NH) 1680, 1661 $cm^{-1}$ (2x C=O)

**$^1$H NMR (400 MHz) (DMSO-$d_6$) δ** 10.41 (1H, s, NH), 8.50 (1H, d, *J*= 6.2 Hz, NH), 7.66 (1H, dd, *J*= 7.8 and 1.5 Hz, ArH), 7.51 (1H, dt, *J*= 7.4 and 1.5 Hz, ArH), 7.32-7.16 (6H, m, ArH), 7.10 (1H, d, *J*= 8.1 Hz, ArH), 3.89 (1H, m, *J*= 7.1 Hz, C*H*CO), 3.13 (1H, dd, *J*= 9.2 and 3.2 Hz, PhC*H*H), 2.85 (1H, dd, *J*= 9.2 and 3.3 Hz, PhCH*H*).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 171.30 (C=O), 167.70 (C=O), 137.94 (Ar), 136.75 (Ar), 132.24 (Ar), 130.36 (Ar), 129.35 (Ar), 128.17 (Ar), 126.35 (Ar), 123.98 (Ar), 120.96 (Ar), 53.87 (CH), 33.29 ($CH_2$).

The data is identical to the literature[280].

### 3.4.1.7. Synthesis of 2-phenylethyl-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid ethyl ester [281].




**400** **401** **402**

**Scheme 3.75**

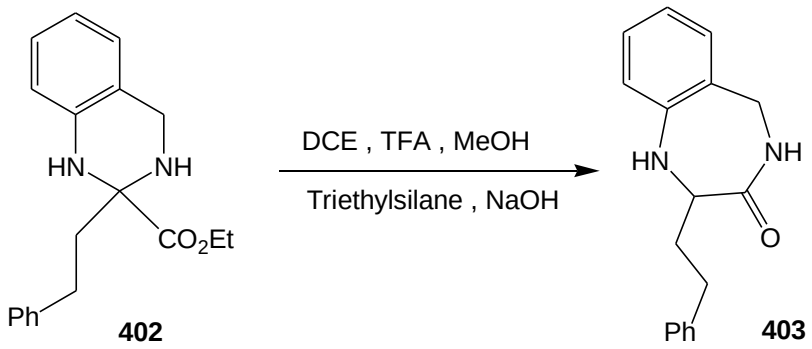
A solution of 2-aminobenzylamine (1.2 g, 10 mmol) and ethyl 2-oxo-4-phenylbutyrate (1.9 ml, 10 mmol, 1 eq.) in 50 ml of toluene was heated at reflux for 18 h using a Dean-Stark apparatus for removal of water. The solvent was then removed under reduced pressure to give the ester crude product as a brown oil (4.20 g), which was used without further processing in the next step.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.34-7.20 ( 5H, m, ArH), 7.19 (1H, s, NH), 7.07 (1H, td, *J*= 6.4 and 1.0 Hz, ArH), 6.94 (1H d, *J*= 7.4 Hz, ArH), 6.74 (1H, td, *J*= 6.4 and 1.0 Hz, ArH), 6.63 (1H, d, *J*= 7.4 Hz, ArH), 4.56 (1H, s, NH), 4.28-4.18 (2H, m, $CH_2CH_3$), 4.04 (1H, d, *J*= 16.5 Hz, Ar$CH_2$NH), 3.99 (1H, d, *J*= 16.5 Hz, Ar$CH_2$NH), 2.87-2.63 (2H, m, $CH_2$), 2.24-2.13 (2H, m, $CH_2$), 1.31 (3H, t, *J*= 7.1 Hz, $CH_2CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 173.34 (C=O), 141.79 (C), 141.03 (C), 128.40 (CH), 128.27 (CH), 127.41 (CH), 126.12 (CH), 125.34 (CH), 120.31 (CH), 118.52 (CH), 115.66 (C), 61.91 (C), 42.56 (CH2), 41.03 (CH2), 30.98 (CH2), 29.56 (CH2), 14.33 (CH3).

As reported in the literature[281].

### 3.4.1.8. Synthesis of 2-phenylethyl-2,3,4,5-terahydrobenzodiazepine-3-one [281].




**Scheme 3.76**

To a stirred solution of crude tetrahydroquinazoline (4.20 g, 13.5 mmol) in 1,2-DCE (40 ml) was added TFA (10 ml) at 0 $^{o}$C, followed by triethylsilane ( 4 ml, 25 mmol, 1.9 eq.), and the reaction mixture was allowed to warm to rt over 2 h. The solvent was then removed under reduced pressure and the residue was dissolved in methanol (50 ml). To this stirred solution at 0 $^{o}$C was added 1N NaOH to adjust the pH to 13. After 18 h, the precipitates were collected to give the benzodiazepine as a yellow solid (1.4 g, 40 %), m.p. 143-146 $^{o}$C.

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3262, 3014, 2893, 1666, 1600, 1487, 1450.

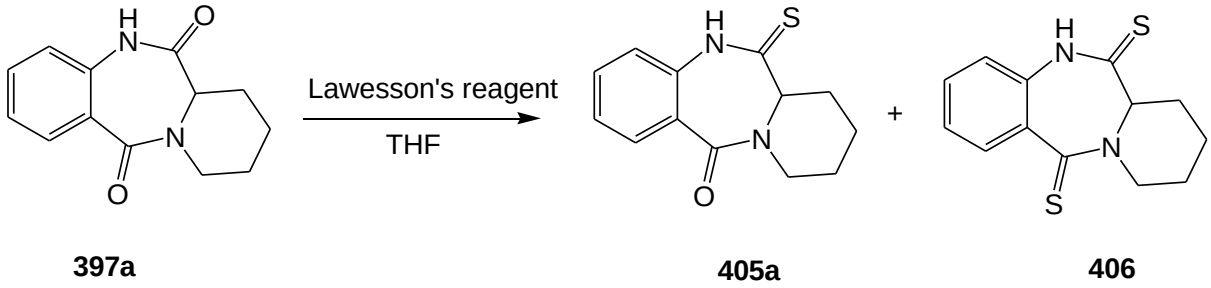
**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.34-7.21 (5H, m, ArH), 7.09 (1H, td, *J*= 7.2 and 1.0 Hz, ArH), 6.91 (1H, d, *J*= 7.2, Hz, ArH), 6.77 (1H, br, *NH*CO), 6.65 (1H, t, *J*= 7.2 Hz, ArH), 6.54 (1H, d, *J*= 7.9 Hz, ArH), 4.87 (1H, dd, *J*= 16.4 and 6.6 Hz, Ar*CH*$_2$NH), 4.36 (1H, t, *J*= 6.3 Hz, C*H*CO), 3.87 (1H, dd, *J*= 16.4 and 6.6 Hz, Ar*CH*$_2$NH), 3.46 (1H, s, NH), 2.94-2.77 (2H, m, PhCH$_2$*CH*$_2$), 2.40-2.31 (1H, m, Ph*CH*$_2$), 1.99-1.90 (1H, m, Ph*CH*$_2$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 172.62 (C=O), 145.43 (C), 141.22 (C), 129.26 (CH), 128.82 (CH), 128.57 (CH), 128.55 (CH), 126.17 (CH), 121.34 (CH), 118.39 (CH), 117.65 (C), 53.81 (CH), 45.37 ($CH_2$), 32.58 ($CH_2$), 32.23 ($CH_2$).

**MS. (ESI, *m/z*),** 289.1311 $(M+Na)^+$, calculated for $C_{17}H_{18}N_2ONa$, measured 289.1301.

Consistent with that reported in literature[281].

### 3.4.1.9. Synthesis of *1,2,3,11a-Tetrahydro-10H-picolo[2,1-c][1,4]benzodiazepine-5,11-dithione* and *1,2,3,11a-Tetrahydro-10H-picolo[2,1-c][1,4]benzodiazepine-5-one-11-thione*.




**397a** **405a** **406**

**Scheme 3.77**

To 1,2,3,11a-tetrahydro-10H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (500 mg, 2.18 mmol) in dry THF (15 ml) was added Lawesson's reagent (882 mg, 2.18 mmol, 1 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^{o}$C for 1h. The solvent was removed by rotary evaporation to yield the crude product mixture as an orange oil. It was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 3/1, Rf = 0.24) to yield a yellow solid (250 mg, 50 %) as the monothionated product and a second solid (Rf = 0.48, 120 mg, 22 %) as the double thionated product.

**Monothione**

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3246 (NH), 1636 (C=O), 1599 (C=S).

**$^{1}$H NMR δ (500 MHz) (DMSO-d$_6$)** 12.3 (1H, s, NH), 7.78 (1H, dd, *J*= 6.6 and 1.6 Hz, ArH), 7.54 (1H, dt, *J*= 6.6 and 1.6 Hz, ArH), 7.32 (1H, dt, *J*= 6.9 and 1.0 Hz, ArH), 7.25 (1H, d, *J*= 8.0, ArH), 4.40 (1H, dd, *J*= 13.2, 3.1 Hz, CH), 4.26 (1H, dd, *J*= 3.9, 12.7 Hz, NCH*H*), 2.78 (1H, td, *J*= 12.8 and 3.9, NC*H*H), 2.15-2.35 (2H, m, $CH_2$), 1.44-1.82 (4H, m, 2 x $CH_2$).

**$^{13}$C NMR δ (125 MHz)** 202.18 (C=S), 166.71 (C=O), 136.66 (Ar), 132.32 (Ar), 130.92 (Ar), 128.64 (Ar), 126.08 (Ar), 121.39 (Ar), 54.72 (CH), 39.08 ($CH_2$), 25.30 ($CH_2$), 23.28 ($CH_2$), 18.93 ($CH_2$).

**HRMS. (ESI, *m/z*),** 269.0719 $(M+Na)^+$ 515.2 $(2M+Na)^+$, calculated for $C_{13}H_{14}N_2SONa$ and was measured 269.0704.

**Dithione**

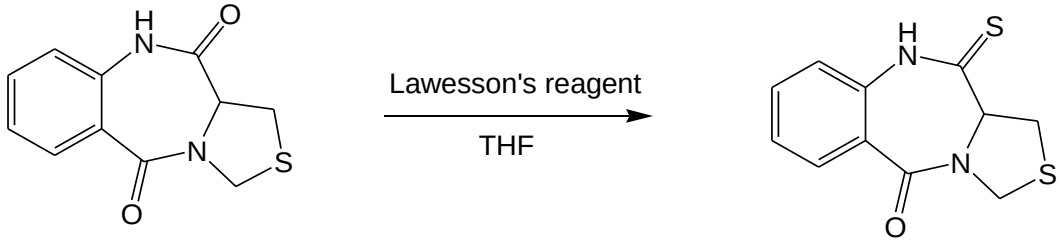
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3246 (NH), 1599, 1508 $cm^{-1}$ (2x C=S)

**$^{1}$H NMR δ (500 MHz) (DMSO-$d_6$)** 12.58 (1H, s, NH), 7.78 (1H, dd, *J*= 6.6 and 1.5 Hz, ArH), 7.56 (1H, dt, *J*= 6.6 and 1.6 Hz, ArH), 7.32 (1H, dt, *J*= 6.9 and 1.0 Hz, ArH), 7.24 (1H, d, *J*= 8.0, ArH), 5.30 (1H, dd, *J*= 10.1, 3.1 Hz, CH), 4.56 (1H, dd, *J*= 3.9, 12.8 Hz, NCH*H*), 2.98 (1H, td, *J*= 12.9 and 3.9, NC*H*H), 2.35-2.15 (2H, m, $CH_2$), 1.82-1.44 (4H, m, 2 x $CH_2$).

**$^{13}$C NMR δ (125 MHz)** 199.39 (C=S), 193.89 (C=S), 135.66 (Ar), 133.98 (Ar), 133.25 (Ar), 132.0 (Ar), 125.88 (Ar), 121.08 (Ar), 60.12 (CH), 47.20 ($CH_2$), 25.25 ($CH_2$), 22.69 ($CH_2$), 17.95 ($CH_2$).

**MS. (ESI, *m/z*),** 285.04626 $(M+Na)^+$, measured for $C_{13}H_{14}N_2S_2ONa$ while calculated was 285.0451.

**3.4.1.10. Synthesis of *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-5-one-11-thione*.**




**397b** **405b**

**Scheme 3.78**

To 1,2,3,10,11,11a-hexahydro-5*H*-thiazolo[4,3-c][1,4]benzodiazepine-5,11-dione (1 g, 4.26 mmol) in dry THF (15 ml) was added Lawesson's reagent (2.067 g, 4.26 mmol, 1.2 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^{o}$C for 1h. The solvent was removed by rotary evaporation to yield the crude product as an orange oil. It was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 3/1, Rf = 0.24) to yield a yellow solid ( 780 mg, 69 %).

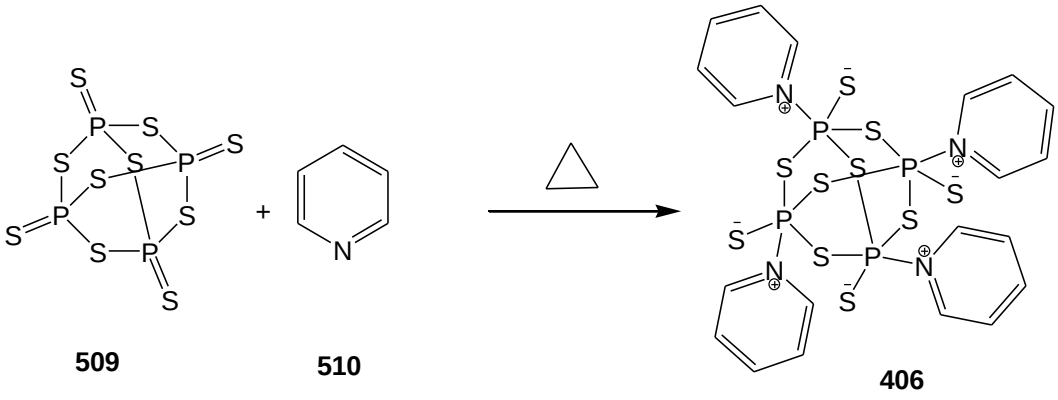
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3430 (NH) 1701 (C=O), 1592 (C=S), 1500, 1470.

**$^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ** 12.68 (1H, s, NH), 7.70 (1H, dd, *J*= 8.5 and 1.5 Hz, ArH), 7.48 (1H, td, *J*= 8.5 and 1.5 Hz, ArH), 7.29 (1H, td, *J*= 8.5 and 1.1 Hz, ArH), 7.08 (1H, d, *J*= 8.0 Hz, ArH), 4.90 (1H, d, *J* = 10.6 Hz, NCH*H*), 4.76 (1H, d, *J* = 10.6 Hz, NC*H*H), 4.34 (1H, dd, *J*= 3.2 and 6.8 Hz, C*H*CO), 3.83 (1H, dd, *J*= 12.4 and 3.2 Hz, SC*H*H), 3.24 (1H, dd, *J*= 12.4 and 6.8 Hz, SCH*H*).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 200.42 (C=S), 164.48 (C=O), 136.81 (Ar), 133.30 (Ar), 130.98 (Ar), 127.18 (Ar), 126.37 (Ar), 122.28 (Ar), 61.38 ($CH_2$), 49.9 ($CH_2$), 34.48 ($CH_2$).

**MS. (ESI, *m/z*),** 273.012675 $(M+Na)^+$ calculated for $C_{11}H_{10}N_2S_2ONa$ and measured 273.012717.

### 3.4.1.11. Synthesis of $P_2S_5$-Pyr. Complex [173].

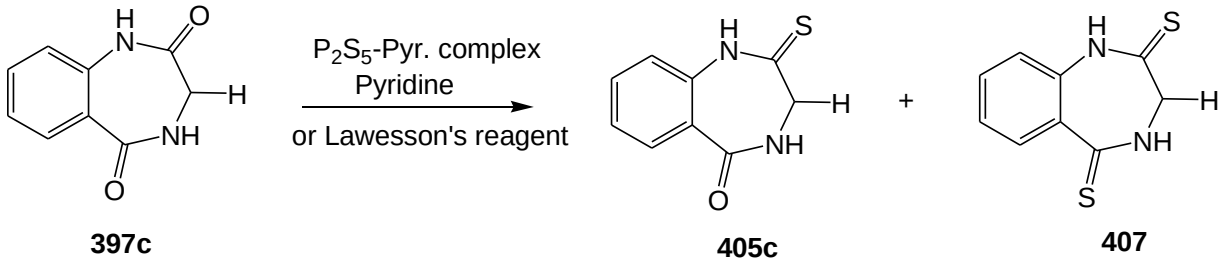



**Scheme 3.79**

Tetraphosphorus decasulfide ($P_4S_{10}$, 4.45g, 10 mmol) was added in portions to dry pyridine (56 ml) at 80 $^{o}$C with stirring. After a period of reflux of 1h a clear yellow solution was obtained, which deposited light yellow crystals when the solution was allowed to cool. After 2 h the crystals were collected, and washed with dry acetonitrile: yield (3.4 g, 45 %); m.p. 167-169 $^{o}$C [173].

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3088, 3044, 1608, 1451, 1197, 1044, 723, 668 cm$^{-1}$, as reported in literature[173].

### 3.4.1.12. Synthesis of *3H-1,4-benzodiazepine-2,5(1H,4H)dithione* [173].




**Scheme 3.80**

**By using $P_2S_5$-pyr. complex (synthesis of dithione).**

To 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (500 mg, 2.84 mmol) in dry pyridine (10 ml) was added $P_2S_5$-Pyr. complex (544 mg, 1.42 mmol, 0.5 eq.) under an inert atmosphere and the mixture was heated at reflux for 2 h. The solvent was removed by rotary evaporation and water (15 ml) was added to the mixture. A solid was quickly formed which was filtered, and washed with water to yield the pure dithionated product as yellow powder (460 mg, 78 %).

**By using Lawesson's reagent (synthesis of monothione).**

To 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (250 mg, 1.42 mmol) in dry THF (10 ml) was added Lawesson's reagent (272 mg, 1.42 mmol, 1 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^oC$ for 1h. The solvent was removed by rotary evaporation to yield the crude product as orange oil. It was purified by column chromatography (PE 40-60 $^oC$ / EtOAc : 5/1, Rf = 0.24) to yield a yellow solid ( 180 mg, 66 % ) as a monothione.

**Monothione**

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3178 (NH), 1670 (C=O), 1536 (C=S), 1474, 1449, 1409.

**$^1$H NMR (400 MHz) (DMSO-$d_6$) δ** 12.38 (1H, s, NH), 8.83 (1H, t, *J*= 4.6 Hz, NH), 7.80 (1H, dd, *J*= 5.2 and 1.1 Hz, ArH), ), 7.57 (1H, dt, *J*= 5.4 and 1.2 Hz, ArH), 7.34 (1H, dt, *J*= 5.6 and 1.0 Hz, ArH), 7.25 (1H, d, *J*= 6.3 Hz, ArH), 3.96 (2H, d, *J*= 4.6 Hz, $CH_2$).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 201.27 (C=S), 167.29 (C=O), 137.04 (Ar), 133.08 (Ar), 130.85 (Ar), 126.72 (Ar), 125.67 (Ar), 121.26 (Ar), 51.58 ($CH_2$).

**Dithione**

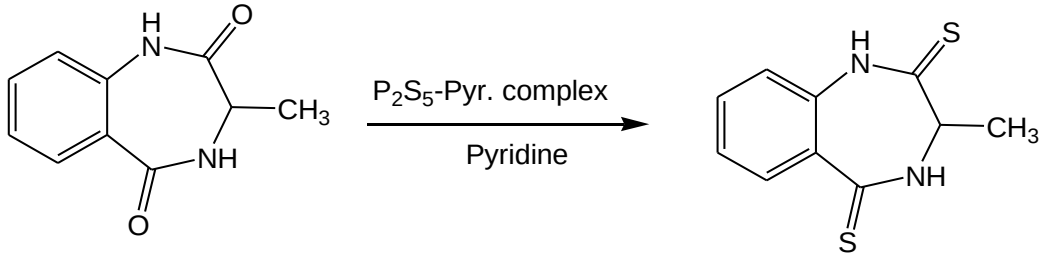
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3178 (NH) 1591, 1547 (2x C=S), 1467, 1392.

**$^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ** 12.51 (1H, s, NH), 11.14 (1H, t, *J*= 5.6 Hz, NH), 8.08 (1H, dd, *J*= 6.7 and 1.3 Hz, ArH), 7.55 (1H, dt, *J*= 6.8 and 1.5 Hz, ArH), 7.21 (1H, t, *J*= 7.2 Hz, ArH), 7.18 (1H, d, *J*= 8.0 Hz, ArH), 3.58 (2H, d, *J*= 5.8 Hz, $CH_2$).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 199.73 (C=S), 196.11 (C=S), 135.18 (Ar), 133.59 (Ar), 132.73 (Ar), 126.04 (Ar), 124.41 (Ar), 121.77 (Ar), 56.25 ($CH_2$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.13. Synthesis of *3-methyl-3H-1,4-benzodiazepine-2,5(1H,4H)dithione* [173].




**397d** **405d**

**Scheme 3.81**

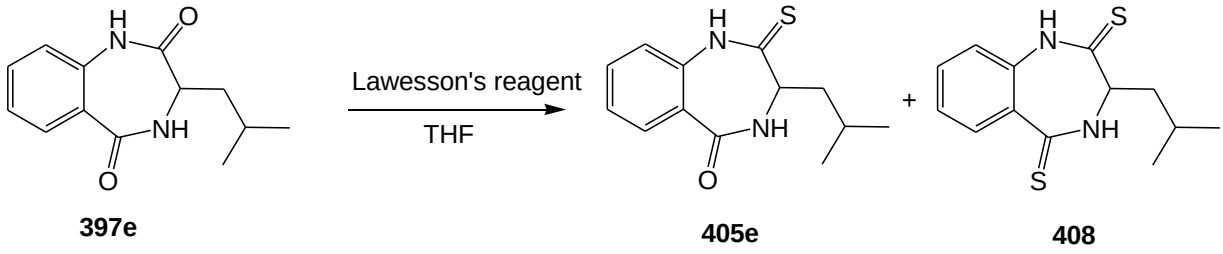
To 3-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (130 mg, 0.684 mmol) in dry pyridine (7 ml) was added $P_2S_5$-Pyr. complex (157 mg, 0.342 mmol, 0.5 eq.) under an inert atmosphere and the mixture was heated at reflux for 2 h. The solvent was removed by rotary evaporation and water (15 ml) was added to the mixture. A solid was quickly formed which was filtered, and washed with water to yield the pure product as a yellow powder (40 mg, 27 %).

**$^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ** 10.82 (1H, s, NH), 9.8 (1H, d, *J*= 5.3 Hz, NH), 7.76 (1H, d, *J*= 7.4 Hz, ArH), 7.56 (1H, dt, *J*= 7.2 and 1.6 Hz, ArH), 7.26 (1H, t, *J*= 7.4 Hz, ArH), 7.04 (1H, d, *J*= 7.6 Hz, ArH), 3.77-3.72 (1H, m, CH), 1.24 (3H, d, *J*= 6.8 Hz, $CH_3$).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 198.73 (C=S), 194.43 (C=S), 136.56 (Ar), 133.92 (Ar), 132.17 (Ar), 126.88 (Ar), 124.74 (Ar), 121.56 (Ar), 54.36 (CH), 14.56 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.14. Synthesis of *3-isobutyl-3H-1,4-benzodiazepine-2,5(1H,4H)dithione*




**397e** **405e** **408**

**Scheme 3.82**

To 3-isobutyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (460 mg, 1.98 mmol) in dry THF (15 ml) was added Lawesson's reagent (802 mg, 1.98 mmol, 1 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solvent was removed by rotary evaporation and the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.24) to yield the pure products as light yellow crystals (330 mg, 58 %, dithione) and 64 mg (13 % monothione).

**Dithione**

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3166 (NH) 1582, 1550 (2x C=S)

**$^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ** 12.57 (1H, s, NH), 10.95 (1H, d, *J*= 6.0 Hz, NH), 8.11 (1H, d, *J*= 7.8 Hz, ArH), 7.59 (1H, t, *J*= 7.5 Hz, ArH), 7.36 (1H, t, *J*= 7.5 Hz, ArH), 7.25 (1H, d, *J*= 8.0 Hz, ArH), 4.55 (1H, d, *J*= 7.6 Hz, CH), 2.02 (1H, m, CH), 1.81-1.73 (2H, d, *J*= 6.5 Hz, $CH_2$), 0.92 (3H, d, *J*= 4.8 Hz, $CH_3$), 0.78 (3H, d, *J*= 5.0 Hz, $CH_3$).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 201.78 (C=S), 195.31 (C=S), 134.63 (Ar), 133.56 (Ar), 132.70 (Ar), 132.45 (Ar), 126.14 (Ar), 121.83 (Ar), 58.60 (CH), 55.65 (CH), 24.49 ($CH_2$), 23.36 and 21.87 (2x $CH_3$).

**HRMS. (ESI, *m/z*),** 287.0647 $(M+Na)^+$, calculated for $C_{13}H_{16}N_2S_2Na$ , measured 287.06506.

**Monothione**

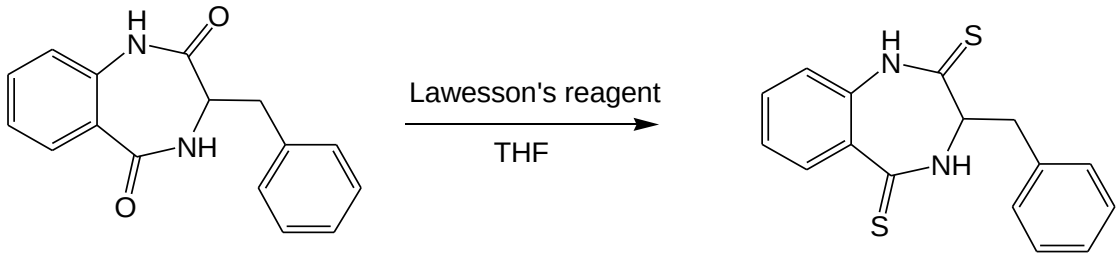
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3166 (NH) 1681 (C=O), 1551 (C=S)

**$^1$H NMR (400 MHz) (DMSO-$d_6$) δ** 12.39 (1H, s, NH), 8.46 (1H, d, *J*= 5.7 Hz, NH), 7.74 (1H, dd, *J*= 6.3 and 1.4 Hz), 7.51 (1H, td, *J*= 7.3 and 1.6 Hz), 7.21 (1H, t, *J*= 7.6 Hz), 7.10 (1H, d, *J*= 8.1 Hz), 3.64-3.55 (1H, m), 1.74-1.67 (1H, m), 1.56 (2H, t, *J*= 7.1 Hz), 0.85 (3H, d, *J*= 6.6 Hz), 0.76 (3H, d, *J*= 6.6 Hz).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 204.19 (C=S), 168.22 (C=O), 137.20 (Ar), 132.69 (Ar), 130.83 (Ar), 126.72 (Ar), 124.38 (Ar), 121.35 (Ar), 50.63 (CH), 36.60 (CH), 24.31 ($CH_2$), 23.31 and 21.89 (2x $CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.15. Synthesis of *3-benzyl-3H-1,4-benzodiazepine-2,5(1H,4H)dithione*




**397f** **405f**

**Scheme 3.83**

To 3-benzyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (160 mg, 0.60 mmol) in dry THF (10 ml) was added Lawesson's reagent (243 mg, 0.60 mmol, 1 eq.) under an inert atmosphere and the mixture was stirred at room temperature for 1 h and then at 60 $^oC$ for 1h. The solvent was removed by rotary evaporation to yield the crude product as an orange oil. It was purified by

column chromatography (PE 40-60 $^{o}$C / EtOAc : 5/1, Rf = 0.24) to yield a yellow solid ( 174 mg, 97 % ).

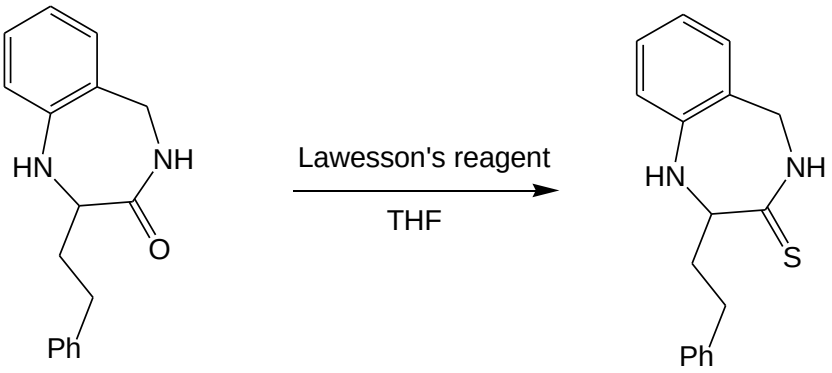
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3169 (NH) 1582, 1520 cm$^{-1}$ (2x C=S), 1462, 1392.

**$^{1}$H NMR (500 MHz) ($CDCl_3$) δ** 10.72 (1H, s, NH), 9.22 (1H, d, *J*= 7.0 Hz, NH), 7.67 (2H, dd, *J*= 6.4 and 1.4 Hz, ArH), 7.51 (2H, dt, *J*= 6.5 and 1.5 Hz, ArH), 7.32 (2H, d, *J*= 7.3 Hz, ArH), 7.22-7.17 (2H, m, ArH), 7.10 (1H, d, *J*= 7.7 Hz, ArH), 3.93-3.85 (1H, m, CH), 3.14 (1H, dd, *J*= 9.3 and 5.0 Hz, PhCH*H*), 2.86 (1H, dd, *J*= 9.3 and 4.9 Hz, PhC*H*H).

**$^{13}$C NMR (125 MHz) ($CDCl_3$) δ** 200.01 (C=S), 196.13 (C=S), 136.06 (Ar), 133.50 (Ar), 132.98 (Ar), 129.25 (Ar), 129.11 (Ar), 127.90 (Ar), 127.43 (Ar), 127.09 (Ar), 126.50 (Ar), 120.84 (Ar), 60.39 (CH), 36.96 ($CH_2$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.16. Synthesis of *2-phenylethyl-2,3,4,5-terahydrobenzodiazepine-3-thione*




**403** **409**

**Scheme 3.84**

To 2-phenylethyl-2,3,4,5-tetrahydrobenzodiazepine-3-one (500 mg, 1.87 mmol) in dry THF (15 ml) was added Lawesson's reagent (378 mg, 0.935 mmol, 0.5 eq.) under an inert atmosphere and the mixture was stirred for 1h at room temperature and then heated at 60 $^{o}$C for 1 h. The solvent was removed by rotary evaporation and the crude mixture was purified

by column chromatography (PE/EA 3:1 ) to yield the pure product as light yellow crystals (350 mg, 93 %).

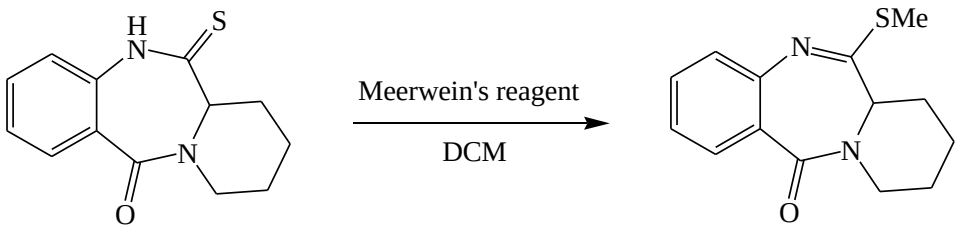
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3264, 3022, 1601 (C=S), 1533, 1480, 1449.

**$^1$H NMR (400 MHz) ($CDCl_3$), δ** 9.06 (1H, t, *J*= 5.5 Hz, *NH*CS), 7.20-7.08 (5H, m, ArH), 6.93 (1H, td, *J*= 6.3 and 1.2 Hz, ArH), 6.71 (1H, d, *J*= 7.4 Hz, ArH), 6.52 (1H, t, *J*= 7.1 Hz, ArH), 6.40 (1H, d, *J*= 8.1 Hz, ArH), 4.93 (1H, dd, *J*= 16.1 and 5.8 Hz, Ar*CH*$_2$NH), 4.39 (1H, t, *J*= 6.3 Hz, NH*CH*), 3.72 (1H, dd, *J*= 16.1 and 7.0 Hz, Ar*CH*$_2$NH), 3.66 (1H, d, *J*= 5.5 Hz, Ar*NH*CH), 2.81-2.67 (2H, m, $CH_2$), 2.42-2.33 (1H, m, $CH_2$), 1.99-1.90 (1H, m, $CH_2$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$), δ** 203.43 (C=S), 144.49 (C), 140.63 (C), 128.83 (CH), 128.41 (CH), 127.83 (CH), 127.71 (CH), 125.49 (CH), 118.37 (CH), 117.78 (CH), 117.36 (C), 55.40 (CH), 47.62 ($CH_2$), 34.81 ($CH_2$), 31.77 ($CH_2$).

**HRMS. (ESI, *m/z*),** 305.1083 calculated for $C_{17}H_{18}N_2S_1Na$ $(M+Na)^+$, found 305.1082.

### 3.4.1.17. Alkylation of *1,2,3,11a-Tetrahydro-10H-picolo[2,1-c][1,4]benzodiazepine-5-one-11-thione*




**405a** **410**

**Scheme 3.85**

To a solution of *1,2,3,11a-tetrahydro-10H-pyrrolo[2,1-c][1,4]benzodiazepine-5-one-11-thione* (200 mg, 0.8 mmol) in anhydrous dichloromethane (10 ml) was added trimethyloxonium tetrafluoroborate (118 mg, 1 eq.) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was then added to an ice cooled 10 % aqueous solution of

potassium carbonate and filtered through celite. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 ml) and combined organic phases were evaporated *in vacuo*. The product was purified by column chromatography using petroleum ether/ethyl acetate (2:1, Rf = 0.54) to yield product 110 mg, 56 %, as a yellow oil.

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 2901, 1631 (C=O), 1573 (C=N), 1488. 1397.

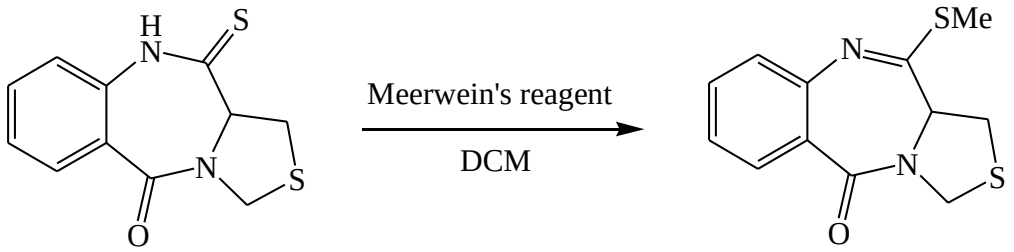
**$^{1}$H NMR δ (500 MHz) ($CDCl_3$)** 7.86 (1H, dd, *J*= 7.8 and 1.5 Hz, ArH), 7.40 (1H, dt, *J*= 8.0 and 1.5 Hz, ArH), 7.17 (1H, dt, *J*= 7.8 and 1.0 Hz, ArH), 7.14 (1H, dd, *J*= 8.0 and 1.0 Hz, ArH), 4.50 (1H, m, CH), 4.08 (1H, dd, *J*= 4.4, 7.1 Hz, $CH_2$), 2.89 (1H, td, *J*= 12.8 and 4.4, $CH_2$), 2.42 (3H, s, $SCH_3$), 2.29-2.15 (2H, m, $CH_2$), 1.95-1.89 (1H, m, $CH_2$), 1.83-1.73 (1H, m, $CH_2$), 1.67-1.56 (2H, m, $CH_2$).

**$^{13}$C NMR δ (125 MHz)** 170.28 (C=O), 167.99 (C=N), 145.52 (Ar), 131.34 (Ar), 130.18 (Ar), 127.16 (Ar), 125.76 (Ar), 124.94 (Ar), 52.58 (CH), 39.10 ($CH_2$), 23.01 ($CH_2$), 23.00 ($CH_2$), 19.71 ($CH_2$), 13.03 ($CH_3$).

**MS. (ESI, *m/z*),** 283.1 $(M+Na)^+$, 543.2 $(2M+Na)^+$, calculated for $C_{14}H_{16}N_2O_1S_1Na$.

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.18. Alkylation of *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-5-one-11-thione*




**405b** **411**

**Scheme 3.86**

To a solution of *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-5-one-11-thione* (100 mg, 0.4 mmol) in anhydrous dichloromethane (10 ml) was added trimethyloxonium tetrafluoroborate (91 mg, 1.5 eq.) and the reaction mixture was heated at

reflux for 2 h. The reaction mixture was then added to an ice cooled 10 % aqueous solution of potassium carbonate and filtered through celite. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 ml) and the combined organic phases were evaporated *in vacuo*. The product was purified by column chromatography using petroleum ether/ethyl acetate 2:1 Rf = 0.40 to yield product 54 mg, 50 %, as a yellow oil.

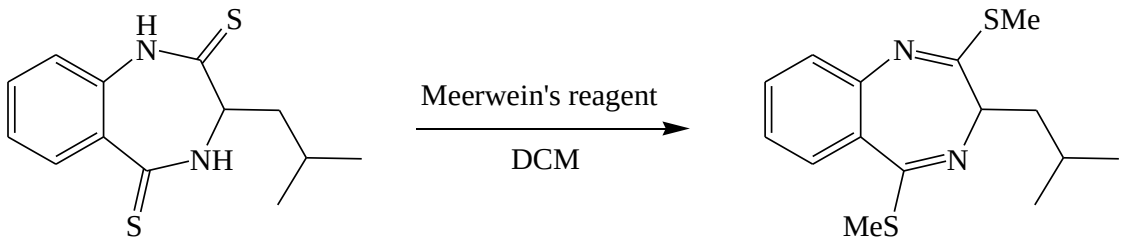
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 2943, 1689 (C=N), 1636 (C=O), 1480, 1399.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.99 (1H, dd, *J*= 8.3 and 1.6 Hz, ArH), 7.52 (1H, td, *J*= 7.9 and 1.6 Hz, ArH), 7.28-7.25 (2H, m, ArH), 4.86 (1H, d, *J*= 10.5 Hz, NCH*H*), 4.76 (1H, d, *J*= 10.5 Hz, NC*H*H), 4.34 (1H, dd, *J*= 3.7 and 7.1 Hz, C*H*$CH_2$), 3.73 (1H, dd, *J*= 12.9 and 3.7 Hz, SCH*H*), 3.39 (1H, dd, *J*= 7.1 and 12.9 Hz, SC*H*H), 2.52 (3H, s, $SCH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 167.70 (C=O), 165.10 (C=N), 145.70 (Ar), 132.11 (Ar), 130.31 (Ar), 126.81 (Ar), 125.61 (Ar), 125.26 (Ar), 58.74 (CH), 49.94 ($CH_2$), 32.28 ($CH_2$), 13.47 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.19. Synthesis of *3-isopropyl-2,5-bis(methylthio)-[1,4]-benzodiazepine*.




**405e** **412**

**Scheme 3.87**

To a solution of *3-isobutyl-3H-1,4-benzodiazepine-2,5(1H,4H)dithione* (250 mg, 0.95 mmol) in anhydrous dichloromethane (10 ml) was added trimethyloxonium tetrafluoroborate (280 mg, 1.89 mmol, 2 eq.) and the reaction mixture was heated at reflux for 2 h. The reaction

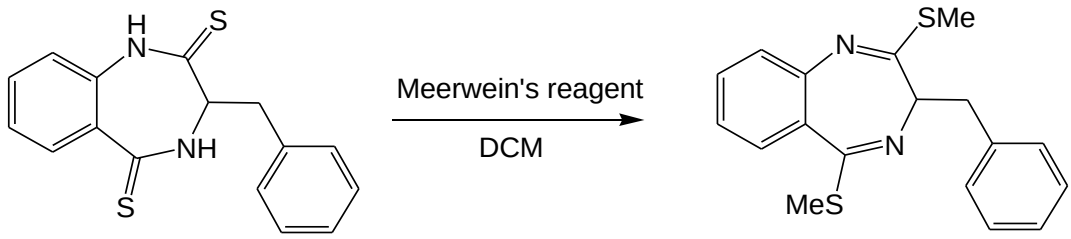
mixture was then added to an ice cooled 10 % aqueous solution of potassium carbonate and filtered through celite. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 ml) and the combined organic phases were evaporated *in vacuo*. The product was purified by column chromatography using petroleum ether/ethyl acetate 3:1 to yield double alkylated product (Rf = 0.48, 192 mg, 69 %) as a yellow oil.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.81 (1H, d, *J*= 7.8 Hz, ArH), 7.47 (1H, t, *J*= 7.5 Hz, ArH), 7.20 (1H, t, *J*= 7.0 Hz, ArH), 7.06 (1H, d, *J*= 8.0 Hz, ArH), 3.62 (1H, dd, *J*= 5.5 and 4.4 Hz, CH), 2.48 (3H, s, $CH_3$), 2.43 (3H, s, $CH_3$), 2.16 (1H, t, *J*= 9.0 Hz, CH), 1.93-1.82 (2H, m, $CH_2$), 0.96 (3H, d, *J*= 5.9 Hz, $CH_3$), 0.80 (3H, d, *J*= 5.9 Hz, $CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 169.63 (C=N), 166.49 (C=N), 136.13 (Ar), 131.92 (Ar), 128.52 (Ar), 127.94 (Ar), 124.28 (Ar), 120.88 (Ar), 61.00 (CH), 39.62 (CH), 24.44 ($CH_2$), 23.55 ($CH_3$), 21.88 ($CH_3$), 14.27 ($CH_3$), 13.44 ($CH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

### 3.4.1.20. Synthesis of *3-benzyl-2,5-bis(methylthio)-3H-[1,4]-benzodiazepine*.




**405f** **413**

**Scheme 3.88**

To a solution of *3-benzyl-3H-1,4-benzodiazepine-2,5(1H,4H)dithione* (180 mg, 0.6 mmol) in anhydrous dichloromethane (10 ml) was added trimethyloxonium tetrafluoroborate (179 mg, 1.20 mmol, 2 eq.) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was then added to an ice cooled 10 % aqueous solution of potassium carbonate and filtered through celite. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 ml) and the combined organic phases were evaporated *in vacuo*. The product

was purified by column chromatography using petroleum ether/ethyl acetate (3:1 Rf = 0.46) to yield the product (182 mg, 93 %) as a yellow oil.

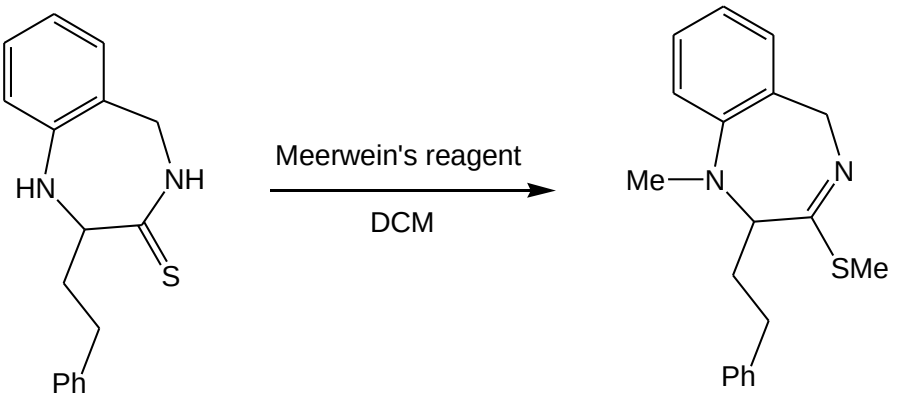
**IR: $_{max}$ (cm$^{-1}$)** 2886, 1579 (2x C=N), 1205, 1127.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.80 (1H, d, *J*= 7.8 Hz, ArH), 7.48 (1H, td, *J*= 8.3 and 1.4 Hz, ArH), 7.34-7.22 (6H, m, ArH), 7.15 (1H, td, *J*= 8.2 and 1.1 Hz, ArH), 3.68 (2H, m, $CH_2$), 3.46 (1H, d, *J*= 10.17 Hz, CH), 2.49 (3H, s, $SCH_3$), 2.44 (3H, s, $SCH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 168.63 (C=N), 166.22 (C=N), 146.78 (C), 138.78 (C), 130.92 (CH-Ar), 129.86 (CH-Ar), 128.17 (CH-Ar), 128.08 (CH-Ar), 127.46 (CH-Ar), 126.62 (CH-Ar), 126.32 (CH-Ar), 123.83 (C), 64.98 (CH), 37.95 ($CH_2$), 14.47 ($CH_3$), 13.40 ($CH_3$).

**MS. (ESI, *m/z*),** 327.1 $(M+H)^+$ calculated for $C_{18}H_{19}N_2S_2$.

### 3.4.1.21. Synthesis of *3-methylthio-1-methyl-2-phenylethyl-4-dihydro-[1,4]-benzodiazepine.*




**409** **414**

**Scheme 3.89**

To a solution of *2-phenylethyl-2,3,4,5-tetrahydrobenzodiazepine-3-thione* (350 mg, 1.24 mmol) in anhydrous dichloromethane (10 ml) was added trimethyloxonium tetrafluoroborate (239 mg, 1.3 eq.) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was then added to an ice cooled 10 % aqueous solution of potassium carbonate and filtered through celite. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 ml) and the combined organic phases were evaporated *in vacuo*. The product

was purified by column chromatography using petroleum ether/ethyl acetate (3:1 Rf = 0.51) to yield the product (220 mg, 60 %) as a yellow oil.

**$^{1}$H NMR (400 MHz) ($CDCl_3$), δ** 7.21-7.12 (5H, m), 7.02 (1H, t, *J*= 7.2 Hz, ArH), 6.90 (1H, d, *J*= 8.0 Hz, ArH), 6.83 (1H, t, *J*= 7.3 Hz, ArH), 4.86 (1H, d, *J*= 15.1 Hz, ArCH*H*N), 4.80 (1H, d, *J*= 15.0 Hz, ArC*H*HN), 3.84 (1H, t, *J*= 5.9 Hz, NC*H*$CH_2$), 2.81 (3H, s, $NCH_3$), 2.62-2.53 (1H, m, PhCH*H*), 2.43-2.35 (1H, m, PhC*H*H), 2.21 (3H, s, $SCH_3$), 2.04-1.85 (2H, m, $CH_2$).

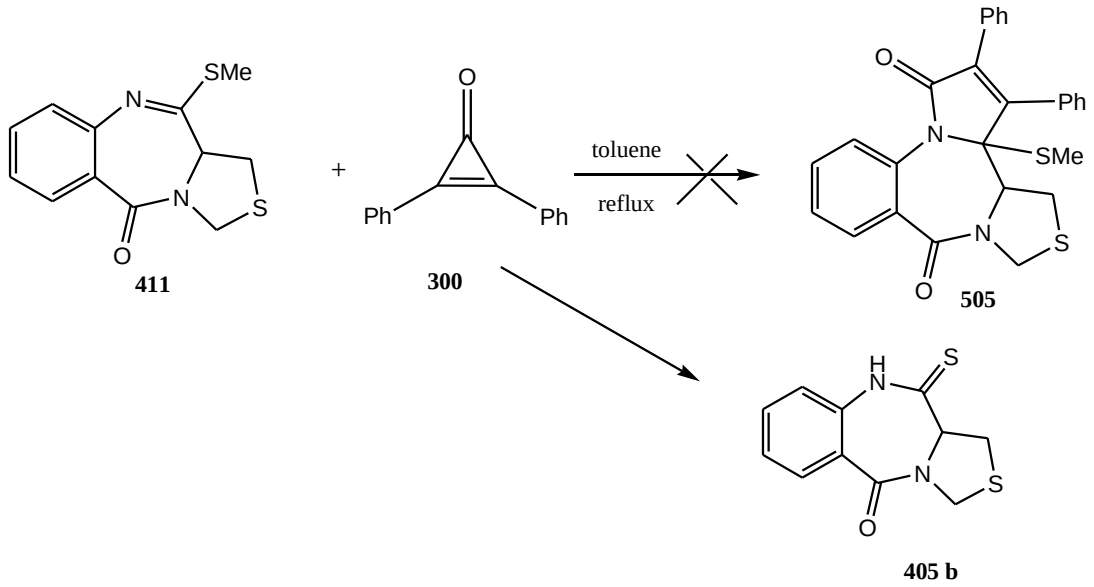
**$^{13}$C NMR (100 MHz) ($CDCl_3$), δ** 166.99 (C=N), 148.68 (C-Ar), 140.90 (C-Ar), 130.69 (CH-Ar), 128.61 (CH-Ar), 127.74 (CH-Ar), 127.42 (CH-Ar), 126.83 (CH-Ar), 125.20 (CH-Ar), 120.96 (CH-Ar), 117.38 (C-Ar), 66.45 (CH), 55.21 ($NCH_3$), 39.70 ($CH_2$), 33.30 ($CH_2$), 31.29 ($CH_2$), 12.16 ($SCH_3$).

"The assigned structure is consistent with the available data. It was not possible to obtain full data for this compound meaning that this assignment remains tentative".

## 3.4.2. Reactivity of benzodiazepines.

### 3.4.2.1. Reactivity of benzodiazepines with cyclopropenones.

#### 3.4.2.1.1. Reactivity of *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-11-methylthio-5-one* with diphenyl cyclopropenone.

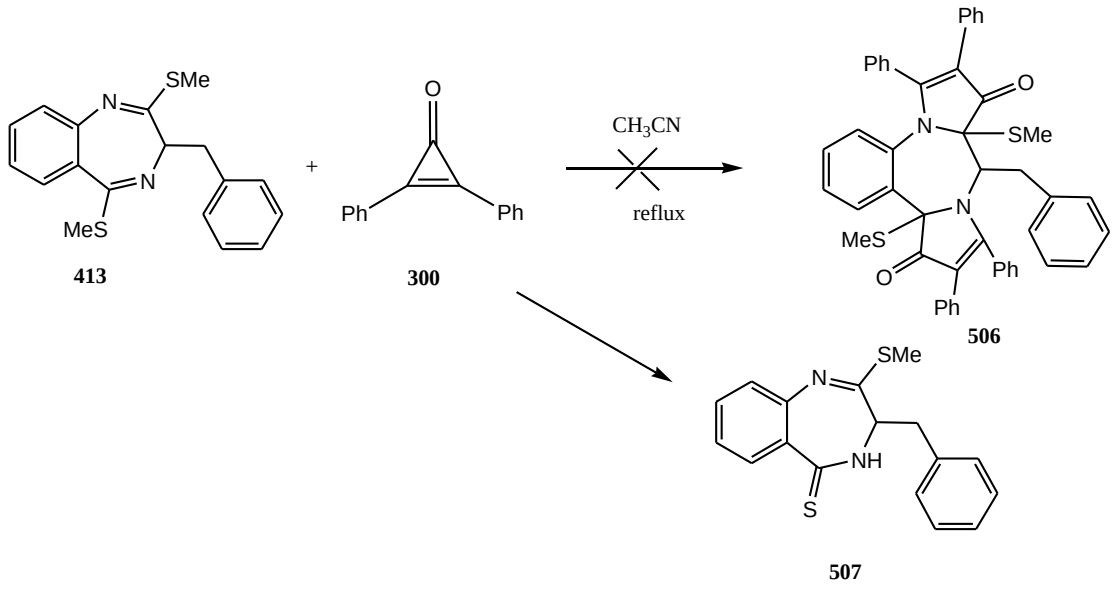



**Scheme 3.90**

To the mixture of *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-11-methylthio-5-one* (100 mg, 0.37 mmol) dry toluene (10 ml) was added diphenylcyclopropenone (DPP) (78 mg, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature for 24 h. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.21 to give *1,2,3,10,11,11a-hexahydro-5H-thiazolo[4,3-c][1,4]benzodiazepine-5-one-11-thione* as a yellow oil (32 mg, 26 %) .

Data as given above for the same compound.

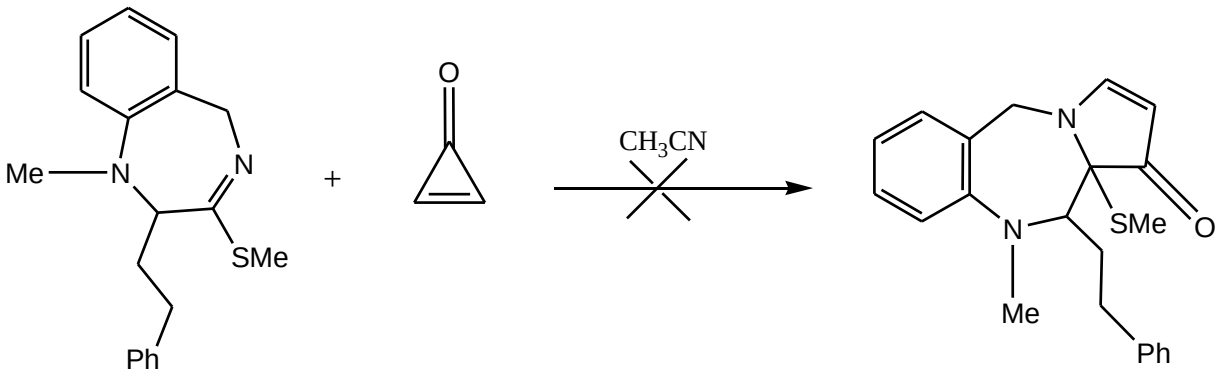
### 3.4.2.1.2. Reactivity of *3-benzyl-2,5-bis(methylthio)-[1,4]-benzodiazepine* with diphenylcyclopropenone.




**Scheme 3.91**

To *3-benzyl-2,5-bis(methylthio)-[1,4]-benzodiazepine* (80 mg, 0.24 mmol) in dry acetonitrile (10 ml) was added diphenylcyclopropenone (DPP) (101 mg, 2 eq.) under a nitrogen atmosphere and the mixture was stirred at room temperature for 24 h and then at reflux for 24 h. The solvent was evaporated *in vacuo* and the mixture was purified by silica gel chromatography using PE 40-60 $^{o}$C / EtOAc : 4/1, Rf = 0.23 to give 3-benzyl-3*H*-1,4-benzodiazepine-2-methylthio-5-thione as yellow oil (21 mg, 27 %).

**3.4.2.1.3. Reactivity of *3-methylthio-2-phenylethyl-2,4-dihydro-1H-benzo-[e][1,4]-benzodiazepine* with cyclopropenone.**



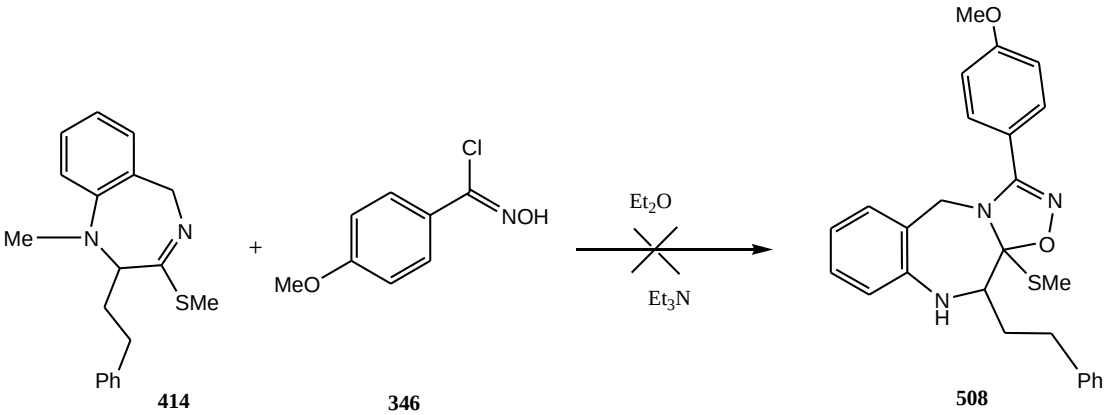

**414** **415** **416**

**Scheme 3.92**

To a solution of *3-methylthio-2-phenylethyl-2,4-dihydro-[1,4]-benzodiazepine* (70 mg, 0.23 mmol) in dry acetonitrile (10 ml) was added cyclopropenone (13 mg, 1 eq.) under a nitrogen atmosphere and the mixture was strirred at room temperature for 24 h. The reaction was monitored by TLC, but no product could be identified. Diphenylcyclopropenone was similarly unreactive.

## 3.4.2.2. Reactivity of benzodiazepines with nitrile oxides

**3.4.2.2.1. Reactivity of *3-methylthio-2-phenylethyl-2,4-dihydro-[1,4]-benzodiazepine* with *p*-methoxy benzohydroximoyl chloride.**

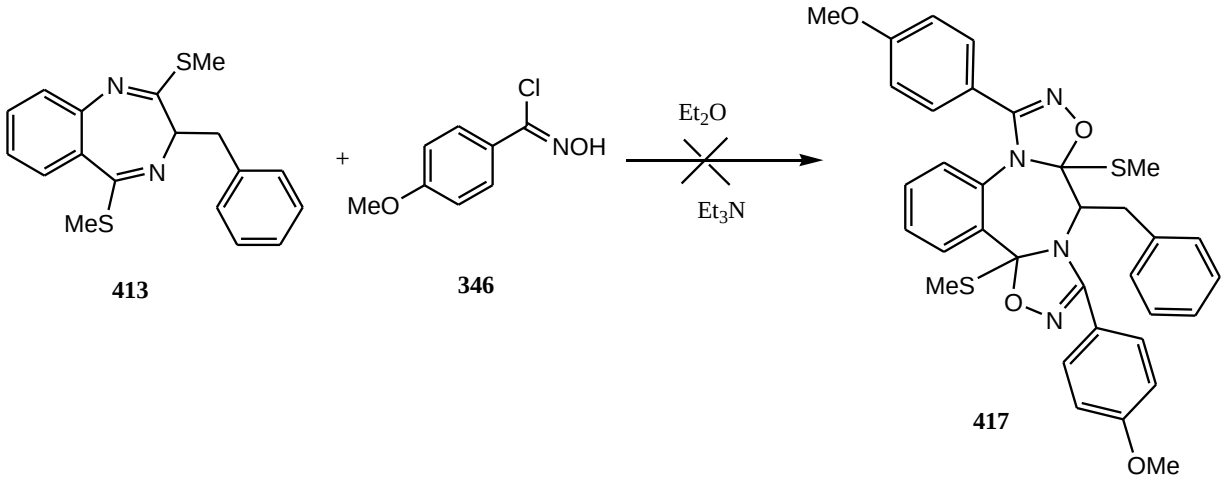



**414** **346** **508**

**Scheme 3.93**

To a solution of *3-methylthio-2-phenylethyl-2,4-dihydro-[1,4]-benzodiazepine* (70 mg, 0.23 mmol) and 4-methoxybenzohydroximoylchloride (1 eq. 43.5 mg) in dry diethyl ether (5 ml) was added triethylamine (1 eq. 23 mg, 33 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and the precipitates were filtered. After removing the solvent *in vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc) to give the dimer of 4-methoxyphenyl nitrile oxide as the only product.

**3.4.2.2.2. Reactivity of *benzyl-2,5-dimethylthio-3H-1,4-benzodiazepine* with *p*-methoxy benzohydroximoyl chloride.**

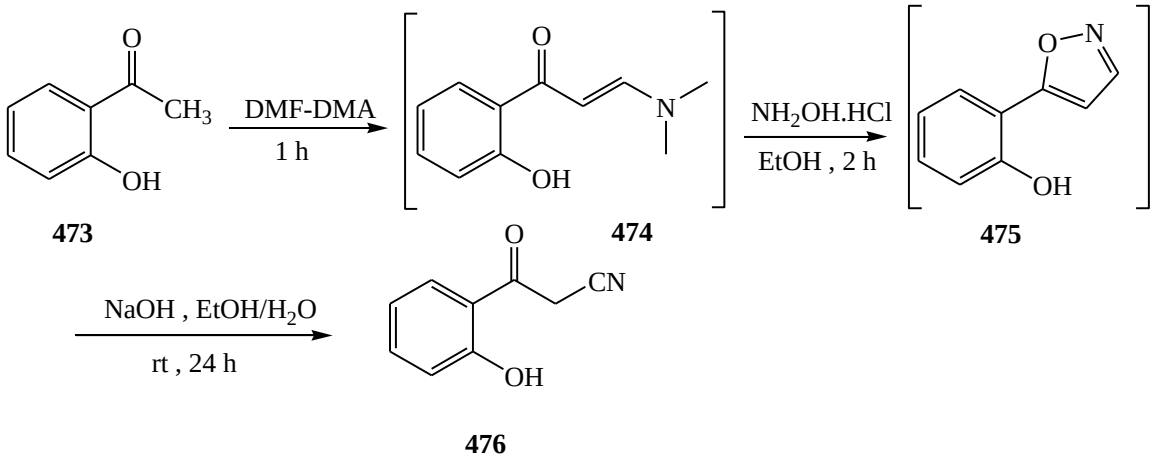



**Scheme 3.94**

To a mixture of *benzyl-2,5-dimethylthio-3H-[1,4]-benzodiazepine* (80 mg, 0.24 mmol) and 4-methoxybenzohydroximoylchloride (2 eq. 88.8 mg) in dry diethyl ether (5 ml) was added triethylamine (2 eq. 48 mg, 67.3 µl) diluted in dry diethyl ether (25 ml) dropwise over 6-7 h at room temperature. The mixture was stirred overnight and the precipitates were filtered. After removing the solvent *in vacuo* the mixture was purified by column chromatography (PE 40-60 $^{o}$C / EtOAc) to give the dimer of 4-methoxyphenyl nitrile oxide as the only product.

## 3.5. Multicomponent reactions : Reactivity of 2-azidobenzaldehyde.

### 3.5.1. Synthesis of 3-(2-hydroxyphenyl)-3-oxopropanenitrile[314].




**473** **474** **475** **476**

**Scheme 3.95**

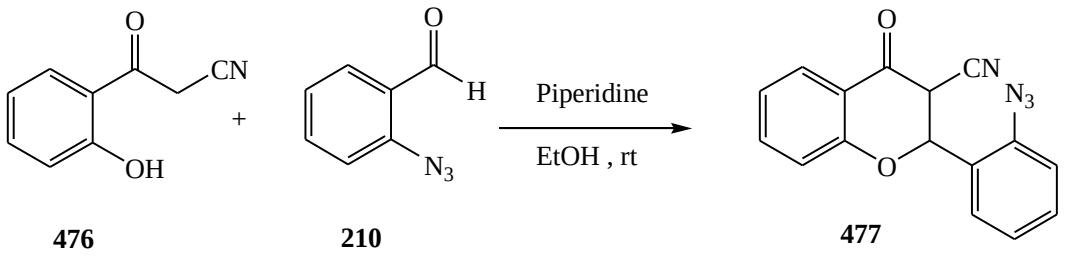
A mixture of 2-hydroxyacetophenone (5 g, 36.7 mmol, 4.42 ml) and dimethylformamide dimethylacetal (DMF-DMA) (4.92 ml, 1 eq.) was heated at reflux for 1 h. On cooling down the precipitates were filtered and dissolved in EtOH and hydroxylamine hydrochloride was added. The mixture was heated at reflux for 2 h and on cooling down the solvent was evaporated under vacuum. A solution of sodium hydroxide in EtOH/$H_2O$ (1:3) was added to the mixture and stirred for 24 h at room temperature. The reaction was monitored by TLC and on completion the mixture was purified with column chromatography (PE/EtOAc : 5/1, Rf = 0.32) to give the product as a yellow oil, 295 mg.

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 11.34 (1H, s, OH), 7.59-7.54 (2H, m, ArH x 2), 7.04 (1H, dd, *J*= 7.8 and 1.0 Hz, ArH), 6.96 (1H, td, *J*= 6.9 and 1.1 Hz, ArH), 4.16 (2H, s, $CH_2$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 192.56 (C=O), 162.67 (C), 138.13 (CH), 129.43 (CH), 119.81 (CH), 119.25 (CH), 117.59 (C), 113.24 (CN), 29.47 ($CH_2$).

The data is identical to literature[314].

### 3.5.2. Synthesis of *2-(2-azidophenyl)-4-oxochroman-3-carbonitrile*[314].




**476** **210** **477**

**Scheme 3.96**

To a mixture of 3-(2-hydroxyphenyl)-3-oxopropanenitrile (150 mg, 0.93 mmol) and 2-azidobenzaldehyde (1 eq. 136 mg) in EtOH, one drop of piperidine was added and the mixture was stirred for 30 min. monitoring the reaction with TLC. The solvent was distilled off and the residue was purified with column chromatography by using pet. ether-ethyl acetate (10:1, Rf = 0.42) to get the product as a yellow coloured oil, 72 mg, 27 % as a mixture of diastereoisomers.

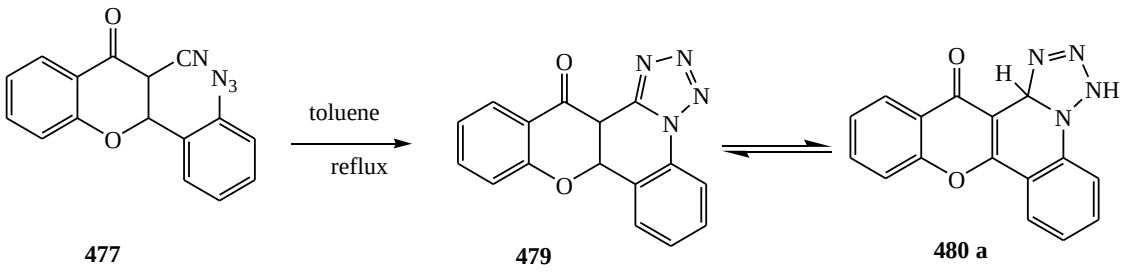
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 2922, 2243 (CN), 2123 ($N_3$), 1700 (C=O), 1640, 1489, 1462, 1297, 1220, 1150, 1113, 1042, 974.

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 7.99 (1H, d, *J*= 8.4 Hz, ArH), 7.94 (1H, d, *J*= 7.9 Hz, ArH), 7.65-7.48 (6H, m, ArH), 7.37-7.24 (6H, m, ArH), 7.17 (1H, d, *J*= 7.9 Hz, ArH), 7.05 (1H, d, *J*= 8.4 Hz, ArH), 5.86 (diastereo, 1H, d, *J*= 12.2 Hz, CH), 5.75 (diastereo, 1H, d, *J*= 2.5 Hz, CH), 4.42 (diastereo, 1H, d, *J*= 12.2 Hz, CH), 3.99 (diastereo, 1H, d, *J*= 2.5 Hz, CH).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 182.62 (C=O), 182.17 (C=O), 161.13 (C-Ar), 160.89 (C-Ar), 137.66 (C-Ar),137.48 (C-Ar), 131.50 (CH-Ar), 130.60 (CH-Ar), 128.68 (CH-Ar), 128.43 (CH-Ar), 128.03 (CH-Ar), 127.90 (CH-Ar), 125.99 (CH-Ar), 125.84 (CH-Ar), 125.61 (CH-Ar), 125.46 (CH-Ar), 123.06 (CH-Ar), 122.90 (CH-Ar), 119.02 (C-Ar), 118.51 (C-Ar),118.23 (C-Ar), 117.91 (C-Ar),112.91 (CN), 112.69 (CN), 76.05 (CH), 74.57 (CH), 45.86 (CH), 43.37 (CH).

**HRMS. (ESI, *m/z*)**, 313.069597 $(M+Na)^+$ calculated for $C_{16}H_{10}N_4O_2Na$, measured 313.069329.

### 3.5.3. Reactivity of *2-(2-azidophenyl)-4-oxochroman-3-carbonitrile*.




**477** **479** **480 a**

**Scheme 3.97**

A solution of *2-(2-azidophenyl)-4-oxochroman-3-carbonitrile* (70 mg, 0.24 mmol) in dry toluene (10 ml) was heated at reflux overnight. The reaction was monitored by TLC and on completion, the solvent was distilled off *in vacuo* and the mixture was purified by using column chromatography with pet. ether-ethyl acetate (5:1, Rf = 0.23) as eluent to give a yellow solid as the single product, 45 mg, 65 %, m.p. 196-200 $^{o}$C.

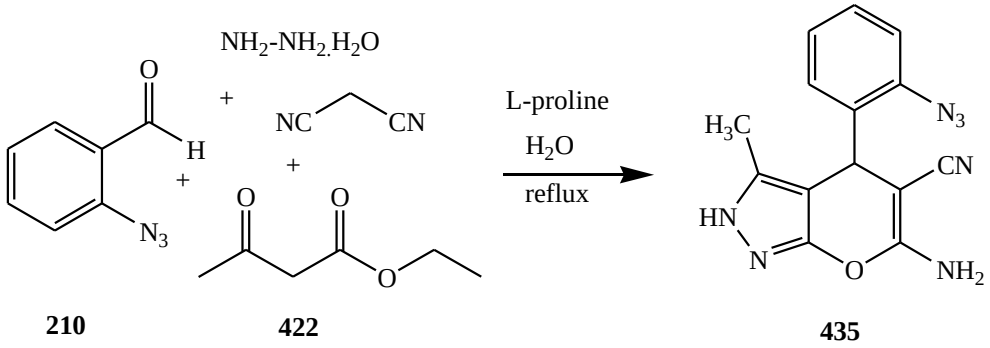
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3353, 2942, 1622, 1586, 1567, 1462, 1443, 1350, 1335, 1247, 1166, 1147, 1093, 902, 844, 754.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 11.78 (1H, s, NH), 8.77 (1H, d, *J*= 8.3 Hz, ArH), 8.22 (1H, s, CH), 8.10 (1H, d, *J*= 8.0 Hz, ArH), 8.02 (1H, t, *J*= 7.8 Hz, ArH), 7.82 (1H, t, *J*= 7.6 Hz, ArH), 7.58 (1H, t, *J*= 7.9 Hz, ArH), 7.51 (1H, d, *J*= 8.0 Hz, ArH), 7.12 (1H, d, *J*= 8.4 Hz, ArH), 6.87 (1H, t, *J*= 7.6 Hz, ArH).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 195.00 (C=O), 163.60 (C), 145.85 (C), 137.93 (CH), 134.80 (CH), 133.17 (CH), 132.83 (CH), 131.33 (C), 130.17 (CH), 128.75 (CH), 123.40 (C), 122.81 (C), 119.27 (CH), 118.92 (C), 118.86 (CH), 117.17 (CH).

**MS. (ESI, *m/z*)**, 313.069597 $(M+Na)^+$ calculated for $C_{16}H_{10}N_4O_2$ and found 313.068899.

**3.5.4. Synthesis of *6-amino-4-(2-azidophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile*[307].**




**210** **422** **435**

**Scheme 3.98**

To a mixture of ethyl acetoacetate (330 mg, 0.32 mL, 2.54 mmol) and hydrazine hydrate (1 eq. 2.54 mmol), in water (5 ml) was added 2-azidobenzaldehyde (1 eq. 369 mg) and malononitrile (1 eq. 168 mg) followed by L-proline (10 mol %, 29.4 mg) and the mixture was heated at reflux for 20 min. On completion of the reaction, the mixture was cooled and then purified using column chromatography with DCM-methanol (5:1, Rf= 0.70) as eluent to afford the desired product as a brown solid, 302 mg, 41 %, m.p. 182-184 $^{o}$C.

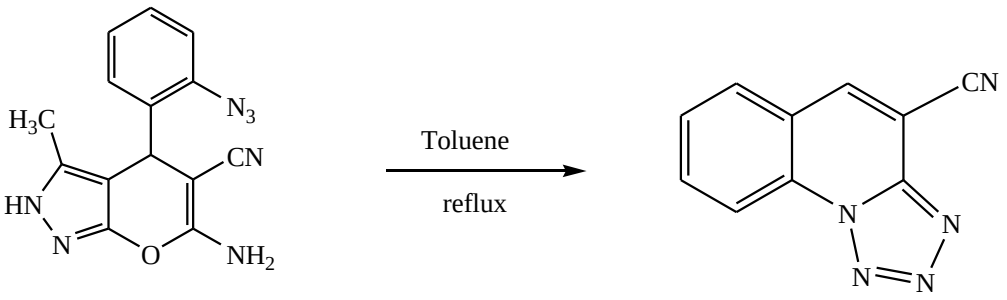
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3323, 3147, 2213, 2125, 1722, 1668, 1594, 1483, 1403, 1291, 1217, 1159, 1043, 925, 866, 845, 755.

**$^{1}$H NMR (400 MHz) (DMSO-d$_6$) δ** 12.15 (1H, NH), 7.35-7.28 (2H, m, ArH), 7.15 (1H, t, *J*= 7.1 Hz, ArH), 7.07 (1H, d, *J*= 7.5 Hz, ArH), 6.88 (2H, s, $NH_2$), 4.86 (1H, s, CH), 1.77 (3H, s, $CH_3$).

**$^{13}$C NMR (100 MHz) (DMSO-d$_6$) δ** 161.73 (C), 155.42 (C), 137.03 (C), 135.87 (C), 135.51 (C), 130.14 (Ar-CH), 129.02 (Ar-CH), 128.55 (Ar-CH), 125.99 (Ar-CH), 121.15 (C), 119.21 (C), 97.53 (CN), 56.63 (CH), 10.03 ($CH_3$).

**HRMS. (ESI, *m/z*)**, 316.091729 $(M+Na)^+$, calculated for $C_{14}H_{11}O_1N_7$, measured 316.091879.

### 3.5.5. Reactivity of *6-amino-4-(2-azidophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile* : Synthesis of tetrazolo[1,5-a]quinoline-4-carbonitrile.




**435** **442**

**Scheme 3.99**

A solution of *6-amino-4-(2-azidophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile* (100 mg, 0.34 mmol) in dry toluene (10 ml) was heated at reflux overnight, and the reaction was monitored by TLC, and on completion the solvent was distilled off *in vacuo* and the mixture was purified by using column chromatography with pet. ether-ethyl acetate (5:1, Rf = 0.72) as eluent to give a brown solid as a product, 35 mg, 75 %, m.p. 267-271 $^{o}$C.

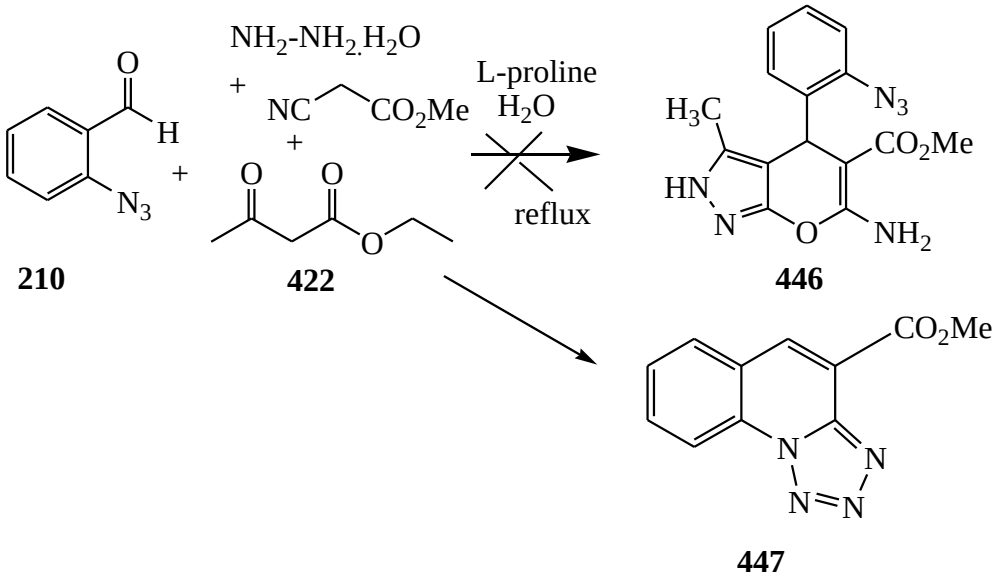
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3400, 2242, 2121, 1657, 1629, 1533, 1472, 1371, 1312, 1221, 1023, 990.

**$^{1}$H NMR (400 MHz) (DMSO-d$_6$) δ** 9.24 (1H, s, CH), 8.74 (1H, d, *J*= 8.0 Hz, ArH), 8.38 (1H, d, *J*= 8.0 Hz, ArH), 8.27 (1H, t, *J*= 7.7 Hz, ArH), 7.99 (1H, t, *J*= 7.7 Hz, ArH).

**$^{13}$C NMR (100 MHz) (DMSO-d$_6$) δ** 146.12 (C), 143.86 (Ar-CH), 135.31 (Ar-CH), 131.89 (C), 131.31 (Ar-CH), 129.42 (Ar-CH), 123.14 (C), 117.01 (CH), 114.54 (C-CN), 97.66 (CN).

**MS. (ESI, *m/z*)**, 218.043716 $(M+Na)^{+}$ calculated for $C_{10}H_5N_5Na$ and found 218.043921.

### 3.5.6. Synthesis of methyl tetrazolo[1,5-a]quinoline-4-carboxylate.




**210** **422** **446** **447**

**Scheme 3.100**

To a mixture of ethyl acetoacetate (330 mg, 0.32 ml, 2.54 mmol), hydrazine hydrate (1 eq. 0.13 ml) in water was added 2-azidobenzaldehyde (1 eq. 369 mg) and methyl cyanoacetate (1 eq. 252 mg, 022 ml) followed by L-proline (10 mol %, 29.4 mg) and the mixture was heated at reflux for 20 min. On completion of the reaction, the mixture was cooled and then purified by using column chromatography with PE / EtOAc : 1/1 (Rf= 0.41) as eluent to afford the product **447** as a yellow solid, 110 mg, 19 %.

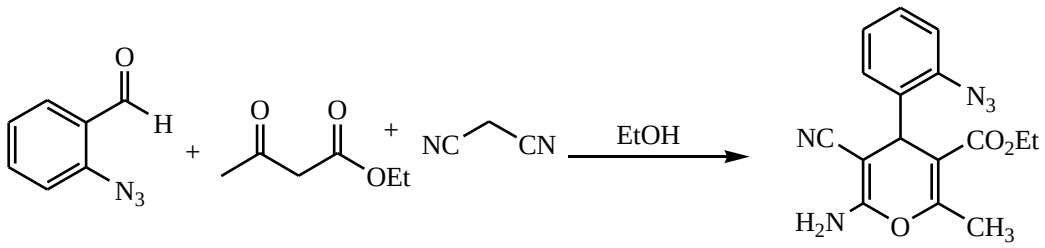
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3397, 1714, 1616, 1592, 1448, 1318, 1254.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 8.80 (1H, s, CH), 8.74 (1H, d, *J*= 8.0 Hz, ArH), 8.13 (1H, d, *J*= 7.9 Hz, ArH), 8.02 (1H, td, *J*= 7.3 and 1.1 Hz, ArH), 7.80 (1H, t, *J*= 7.3 Hz, ArH), 4.15 (3H, s, $CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 163.20 (C=O), 145.58 (C), 138.54 (Ar-CH), 133.75 (Ar-CH), 131.99 (C), 130.54 (Ar-CH), 128.68 (Ar-CH), 122.64 (C), 117.16 (CH), 116.57 (C), 53.42 ($CH_3$).

**MS. (ESI, *m/z*)**, 251.053947 $(M+Na)^+$ calculated for $C_{11}H_8O_2N_4$ and found 251.054593.

**3.5.7. Synthesis of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate*[308].**




**210** **422** **448**

**Scheme 3.101**

To a mixture of 2-azidobenzaldehyde (180 mg, 1.25 mmol), ethyl acetoacetate (1 eq. 162 mg, 0.15 mL, 1.25 mmol) and malononitrile (1 eq. 82.5 mg, 1.25 mmol) in DMF (10 ml) was added triethylamine (1.5 eq. 189 mg, 263 µl, 1.87 mmol) and the mixture was stirred for 48 h at room temperature. After completion of the reaction, the solvent was distilled under vacuum and the mixture was purified by using column chromatography with PE/EA (5:1, Rf = 0.19) as eluent to give a brown coloured oil as product, 212 mg, 59 %.

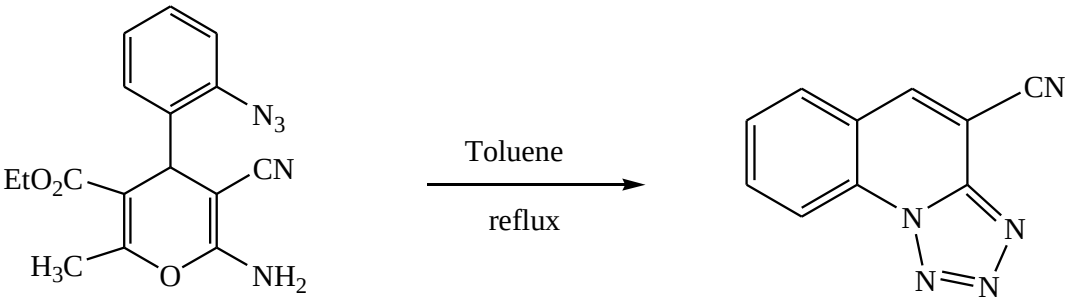
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3322 (m), 2203 (m), 2119 (s), 1704 (s), 1672 (s), 1596 (m), 1485 (m), 1378 (s), 1256 (m), 1214 (s), 1066 (s).

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 7.25 (1H, t, *J*= 7.3 Hz, ArH), 7.14-7.06 (3H, m, ArH), 4.79 (1H, s, CH), 4.57 (2H, bs, $NH_2$), 4.06-3.93 (2H, m, O*C*$H_2$$CH_3$), 2.38 (3H, s, $CH_3$), 1.06 (3H, t, *J*= 7.0 Hz, Me).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 165.79 (C=O), 157.84 (C), 157.79 (C), 137.42 (C), 135.08 (C), 129.60 (Ar-CH), 128.50 (Ar-CH), 125.13 (Ar-CH), 118.91 (C), 118.42 (Ar-CH), 106.79 (C), 61.12 (C), 60.62 (CH), 33.47 ($CH_2$), 18.45 ($CH_3$),13.18 ($CH_3$).

**HRMS (ESI, *m/z*)**, 348.106710 $(M+Na)^+$ calculated for $C_{16}H_{15}N_5O_3Na$, measured 348.106892.

**3.5.8. Reactivity of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate* : Synthesis of tetrazolo[1,5-a]quinoline-4-carbonitrile.**




**448** **442**

**Scheme 3.102**

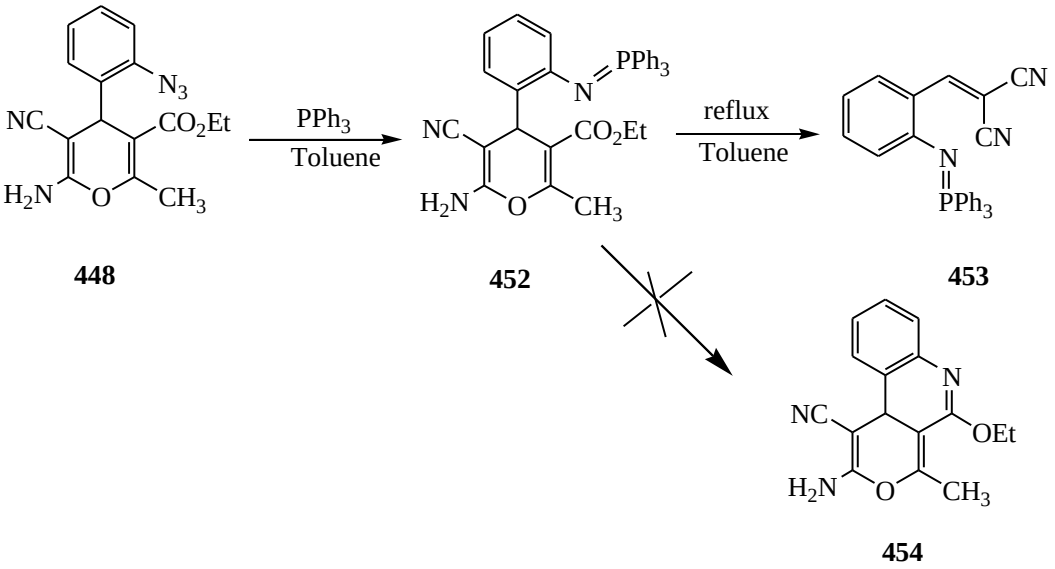
The mixture of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate* (80 mg, 0.24 mmol) in dry toluene (10 ml) was heated at reflux overnight and the reaction was monitored by TLC. On completion the solvent was distilled off *in vacuo* and the mixture was purified by using column chromatography with pet. ether-ethyl acetate (5:1, Rf = 0.72) as eluent to give a brown solid as a product, 35 mg, 75 %, m.p. 267-271 $^{o}$C, identical to that reported above (Scheme 3.99).

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3400, 2242, 1657, 1629, 1533, 1472, 1371, 1312, 1221, 1023, 990.

**$^{1}$H NMR (400 MHz) (DMSO-d$_6$) δ** 9.24 (1H, s, CH), 8.74 (1H, d, *J*= 8.4 Hz, ArH), 8.38 (1H, d, *J*= 8.0 Hz, ArH), 8.27 (1H, t, *J*= 7.7 Hz, ArH), 7.99 (1H, t, *J*= 7.7 Hz, ArH).

**$^{13}$C NMR (100 MHz) (DMSO-d$_6$) δ** 146.12 (C), 143.86 (Ar-CH), 135.31 (Ar-CH), 131.89 (C), 131.31 (Ar-CH), 129.42 (Ar-CH), 123.14 (C), 117.01 (CH), 114.54 (C-CN), 97.66 (CN).

**3.5.9. Reactivity of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate* : Synthesis of 2-(2-aminotriphenylphosphinyl-benzylidene) malononitrile.**




**448** **452** **453** **454**

**Scheme 3.103**

To a solution of *ethyl 6-amino-4-(2-azidophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate* (100 mg, 0.30 mmol) in dry toluene (10 ml) was added triphenylphosphine (1 eq. 81 mg) and the mixture was stirred for 4 h at room temperature. After completion of the reaction, monitored by TLC, the mixture was heated at reflux overnight. The solvent was distilled under vacuum and the mixture was purified by using column chromatography with pet. ether-ethyl acetate (8:1, Rf = 0.64) as eluent to give a white solid as the product, 82 mg, 64 %, m.p. 194-197 $^{o}$C.

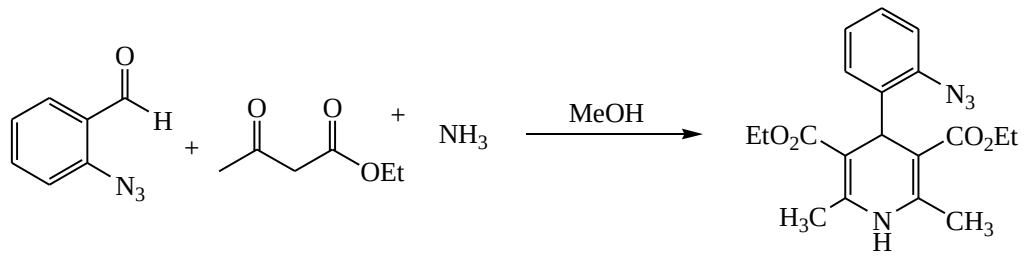
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3042, 2206, 1682, 1626, 1554, 1458, 1413, 1357, 1108, 1043, 730, 533.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 8.15 (1H, s, CH), 7.93 (6H, dd, *J*= 7.8 and 4.5 Hz, ArH), 7.53-7.39 (11H, m, ArH), 7.20 (1H, d, *J*= 8.0 Hz, ArH), 7.10 (1H, t, *J*= 7.1 Hz, ArH).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 160.97 (C), 160.91 (C), 149.32 (C), 143.38 (CH), 143.35 (CH), 133.45 (CH), 133.35 (CH), 131.97 (CH), 131.94 (CH), 131.25 (CH), 130.32 (CH), 129.37 (C), 128.61 (CH), 128.49 (CH), 128.37 (CH), 127.74 (CH), 126.00 (CH), 122.22 (CH), 121.41 (C), 118.94 (C), 105.00 (CN), 104.74 (CN).

**HRMS. (ESI, *m/z*)**, 430.146761 $(M+H)^+$ calculated for $C_{28}H_{21}N_3P$, measured 430.147653.

### 3.5.10 Synthesis of *diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate*[321].




**210** **422** **455**

**Scheme 3.104**

To a mixture of 2-azidobenzaldehyde (735 mg, 5.0 mmol) and ethyl acetoacetate (2 eq. 1.3 g, 1.26 mL, 10 mmol) in MeOH (15 ml) was added 20 % ammonia soln. in water (5 ml) and the mixture was heated at reflux for 24 h. After completion of the reaction, the solvent was distilled under vacuum and the mixture was purified by using column chromatography with PE/EA (5:1, Rf = 0.25) as eluent to give a brown solid as the product, 861 mg, 46 %, m.p. 82-85 $^{o}$C.

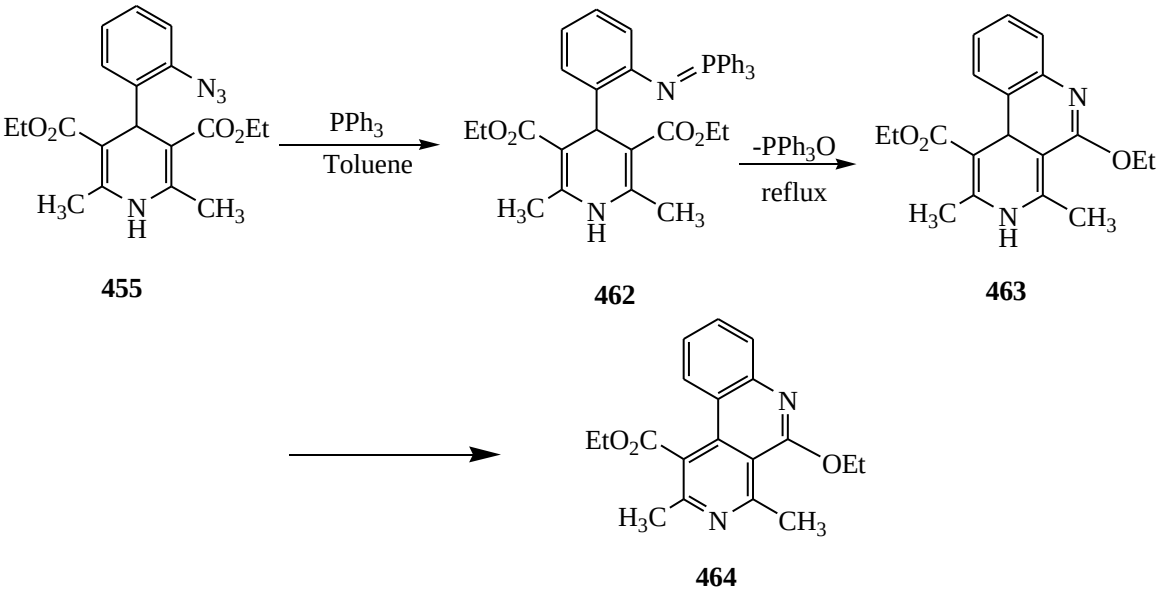
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3320, 2101, 1677, 1618, 1579, 1483, 1433, 1384, 1274, 1207, 1095.

**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 7.30 (1H, t, *J*= 7.0 Hz, ArH), 7.16 (1H, t, *J*= 7.6 Hz, ArH), 7.08-6.99 (2H, m, ArH), 5.80 (1H, bs, NH), 4.08 (4H, m, 2x$CH_2$), 3.61 (1H, s, CH), 2.29 (6H, s, 2x$CH_3$), 1.20 (6H, t, *J*= 7.1 Hz, 2x$CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 167.73 (C=O), 144.24 (C), 139.84 (C), 136.57 (C), 131.11 (CH), 127.55 (CH), 125.01 (CH), 118.20 (CH), 103.47 (C), 60.12 (CH), 59.73 ($CH_2$), 19.52 ($CH_3$), 14.18 ($CH_3$).

**MS. (ESI, *m/z*)**, 393.15513 $(M+Na)^+$ calculated for $C_{19}H_{22}N_4O_4Na$ and measured 393.15332.

**3.5.11. Reactivity of *diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate* : Synthesis of ethyl 5-ethoxy-2,4-dimethyl-[2,7]-naphthyridine-1-carboxylate.**




**455** **462** **463**

**464**

**Scheme 3.105**

To a solution of *diethyl 4-(2-azidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate* (240 mg, 0.64 mmol) in dry toluene (10 ml) was added triphenylphosphine (1 eq. 170 mg) and the mixture was stirred for 4 h at room temperature. After completion of the reaction, monitored by TLC, the mixture was heated at reflux overnight. The solvent was distilled under vacuum and the mixture was purified using column chromatography with PE/EA (4:1, Rf = 0.38) as eluent to give a white solid as the product, 110 mg, 53 %, 106-109 $^{o}$C.

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 2922, 1714, 1582, 1573, 1550, 1455, 1306, 1237, 1143.

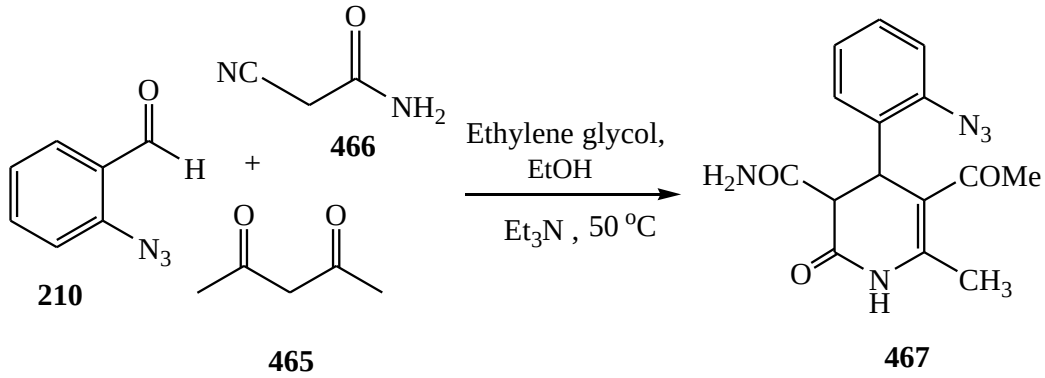
**$^{1}$H NMR (400 MHz) ($CDCl_3$) δ** 8.01 (1H, d, *J*= 8.4 Hz, ArH), 7.81 (1H, d, *J*= 8.2 Hz, ArH), 7.65 (1H, t, *J*= 7.3 Hz, ArH), 7.35 (1H, t, *J*= 7.5 Hz, ArH), 4.65 (2H, q, *J*= 7.1 Hz, $CH_2$), 4.53 (2H, q, *J*= 7.1 Hz, $CH_2$), 3.13 (1H, s, $CH_3$), 2.70 (3H, s, $CH_3$), 1.54 (3H, t, *J*= 7.0 Hz, $CH_3$), 1.39 (3H, t, *J*= 7.2 Hz, $CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 170.91 (C=O), 160.01 (C), 159.09 (C), 153.66 (C), 145.31 (C), 138.83 (C), 130.03 (CH), 127.84 (CH), 125.01 (CH), 124.05 (CH), 121.45 (C), 119.48

(C), 113.04 (C), 62.65 ($CH_2$), 62.22 ($CH_2$), 28.93 ($CH_3$), 22.80 ($CH_3$),14.51 ($CH_3$), 13.91 ($CH_3$).

**MS. (ESI, *m/z*)**, 325.154669 $(M+H)^+$ calculated for $C_{19}H_{21}O_3N_2$ and found 325.154339.

### 3.5.12. Synthesis of *5-acetyl-4-(2-azidophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxamide*[310].




**Scheme 3.106**

To a mixture of 2-azidobenzaldehyde (180 mg, 1.25 mmol), cyanoacetamide (840 mg, 10 mmol) and acetyl acetone (750 mg, 08 ml, 7.5 mmol) in ethylene glycol (5 ml) and ethanol (5 ml) was added triethylamine (1.5 eq. 15 mmol, 2.1 ml) and the mixture was stirred at 50 °C for 24 h. After completion of the reaction, the mixture was purified using column chromatography with PE/EA (3:1, Rf= 0.28) as eluent to afford the desired product as a brown oil, 242 mg, 65 %.

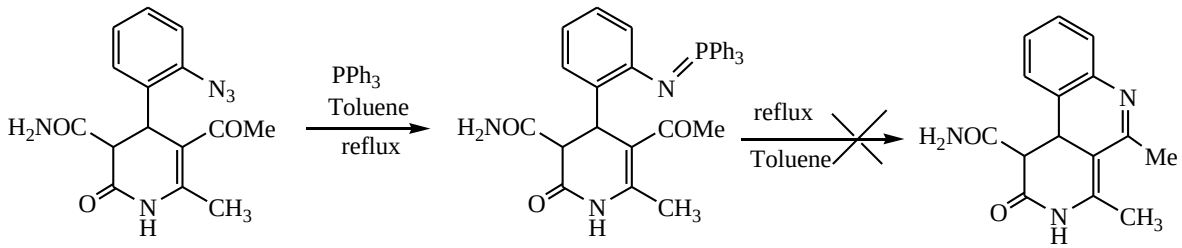
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3361, 3212, 2979, 2124, 1703, 1680, 1581, 1483, 1386, 1365, 1275, 1205.

**$^1$H NMR (400 MHz) (DMSO-$d_6$) δ** 10.06 (1H, s, NH), 7.39-7.30 (2H, m, ArH), 7.22 (2H, bs, $NH_2$), 7.12 (1H, t, *J*= 7.2 Hz, ArH), 6.96 (1H, d, *J*= 7.7 Hz, ArH), 4.58 (1H, bs, CH), 3.26 (1H, bs, CH), 2.20 (3H, s, $CH_3$), 1.99 (3H, s, $CH_3$).

**$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ** 196.82 (C=O), 168.80 (C=O), 167.45 (C=O), 147.58 (C), 137.57 (C), 131.49 (C), 129.27 (CH), 127.72 (CH), 125.61 (CH), 119.67 (CH), 112.45 (C), 54.00 (CH), 37.45 (CH), 30.03 ($CH_3$), 19.14 ($CH_3$).

**MS. (ESI, *m/z*)**, 336.106710 $(M+Na)^+$ calculated for $C_{15}H_{15}O_3N_5$ and found 336.106398.

### 3.5.13. Reactivity of *5-acetyl-4-(2-azidophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxamide*.

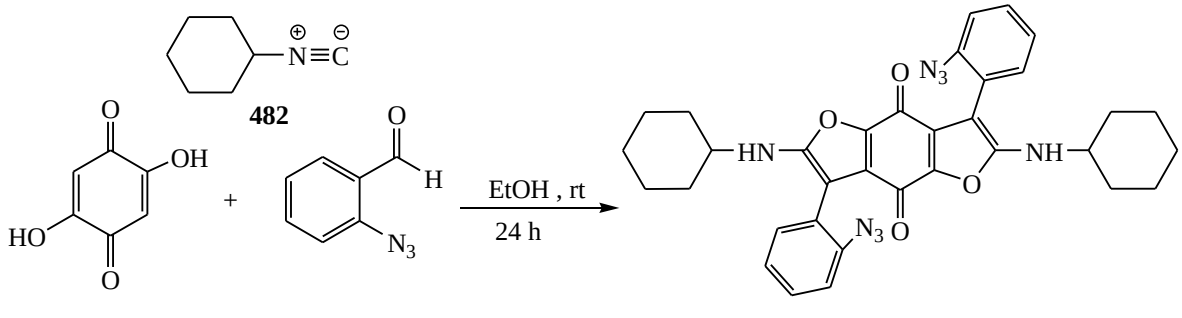



**467** **471** **472**

**Scheme 3.107**

To a solution of *5-acetyl-4-(2-azidophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxamide* (100 mg, 0.39 mmol) in dry toluene (10 ml) was added triphenylphosphine (1 eq. 89 mg) and the mixture was stirred for 4 h at room temperature. After completion of the reaction, monitored by TLC, the mixture was heated at reflux overnight and monitored by TLC which showed no product other than triphenylphosphine oxide confirming that compound had decomposed.

### 3.5.14. Synthesis of *2,6-bis (cyclohexylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione*[315].




**481** **482** **210** **483**

**Scheme 3.108**

To a stirred solution of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (119 mg, 0.85 mmol) and 2-azidobenzaldehyde (2 eq. 250 mg) in ethanol (10 ml) was added cyclohexyl isocyanide (2 eq. 185 mg, 211 µl). After stirring the mixture at room temperature for 24 h, the solvent was removed under vacuum and the residue was purified by column chromatography using

PE/EA (4:1, Rf = 0.32) as eluent. After removal of the solvent, the product was obtained as a black oil, 70 mg, 13 %.

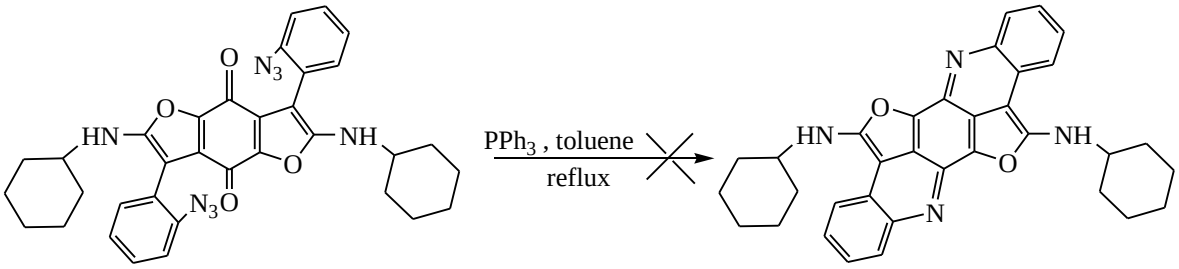
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3421 (NH), 2933, 2854, 2124 ($N_3$), 1739 (C=O), 1662, 1592, 1527, 1450, 1274.

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 7.41 (2H, d, *J*= 7.2 Hz, ArH), 7.34 (4H, m, ArH), 7.16 (2H, d, *J*= 7.7 Hz, ArH), 6.38 (2H, bs, 2 x NH), 3.75-3.70 (2H, m CH), 1.94-1.56 (8H, m), 1.42-1.06 (12H, m).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 170.89 (C=O), 136.80 (C), 131.56 (C), 129.43 (C), 128.56 (C), 128.07 (CH), 126.99 (CH), 125.53 (CH), 118.06 (CH), 48.48 (CH), 32.87 ($CH_2$), 32.64 ($CH_2$), 25.41 ($CH_2$), 24.60 ($CH_2$), 24.54 ($CH_2$).

It is difficult to get exact $^{13}$C NMR of this and related compounds[315], that's why this assigned structure is proposed and may not be correct.

### 3.5.15. Reactivity of *2,6-bis (cyclohexylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione*.

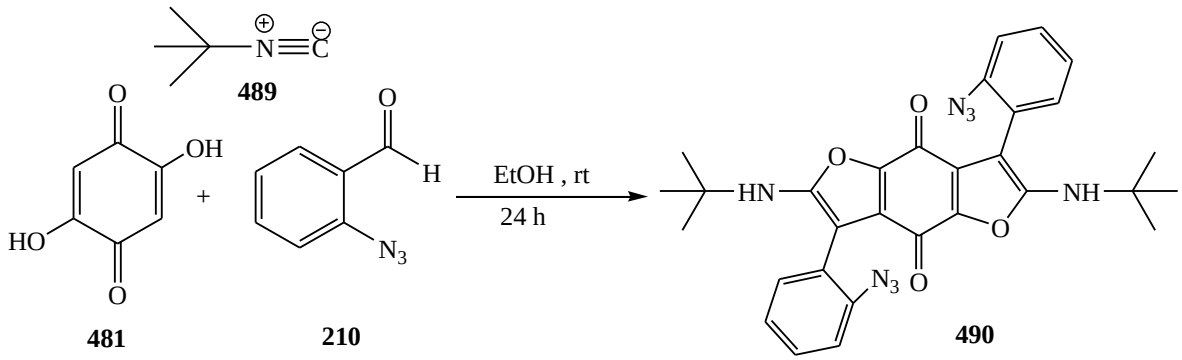



**483** **488**

**Scheme 3.109**

To a solution of *2,6-bis (cyclohexylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione* (70 mg, 0.117 mmol) in dry toluene (10 ml) was added triphenylphosphine (2 eq. 60 mg) and the mixture was stirred for 4 h at room temperature. After monitoring by TLC, which showed no reaction, the mixture was heated at reflux overnight and monitored by TLC which showed no product other than triphenylphosphine oxide confirming that the compound had decomposed at higher temperature.

### 3.5.16. Synthesis of *2,6-bis (tert-butylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione*[315].




**Scheme 3.110**

To a stirred solution of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (140 mg, 0.85 mmol) and 2-azidobenzaldehyde (2 eq. 250 mg) in ethanol (10 ml) was added *tert*-butylisocyanide (2 eq. 141 mg ). After stirring the mixture at room temperature for 24 h, the solvent was removed under vacuum and the residue was purified by column chromatography using PE/EA (5:1, Rf = 0.42) as eluent. After removal of the solvent under vacuum, the product was obtained as dark brown oil, 72 mg, 15 %.

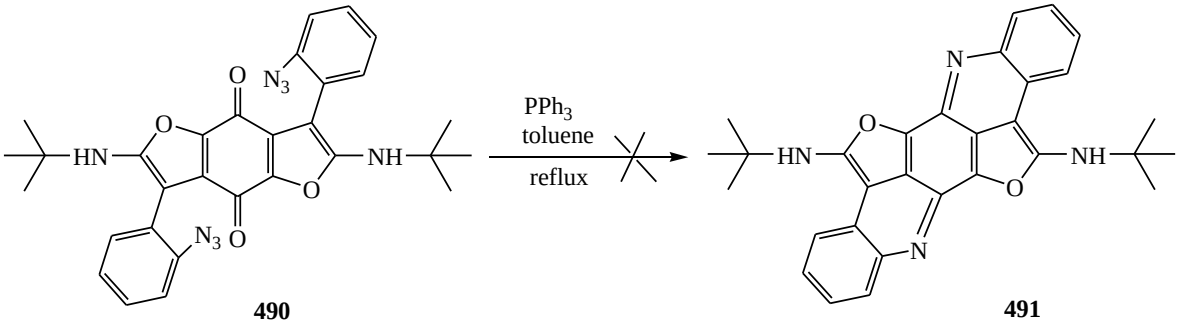
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3452 (NH), 2963, 2126 ($N_3$), 1737 (C=O), 1654, 1590, 1519, 1458, 1364, 1293.

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 7.43 (2H, d, *J*= 7.6 Hz, ArH), 7.35 (4H, m, ArH), 7.18 (2H, d, *J*= 7.4 Hz, ArH), 6.29 (2H, s, 2 x NH), 1.32 (18H, s, 6x$CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 170.87 (C=O), 136.83 (C), 131.54 (C), 129.41 (C), 128.54 (C), 128.05 (CH), 126.96 (CH), 125.52 (CH), 118.08 (CH), 51.55 (C), 29.61 ($CH_3$), 28.67 ($CH_3$), 28.19 ($CH_3$).

It is difficult to get exact $^{13}$C NMR of this and related compounds[315], that's why this assigned structure is proposed and may not be correct.

### 3.5.17. Reactivity of *2,6-bis (tert-butylamino)-3,7-bis (2-azidophenyl) benzofuro[5,6-b]furan-4,8-dione*.

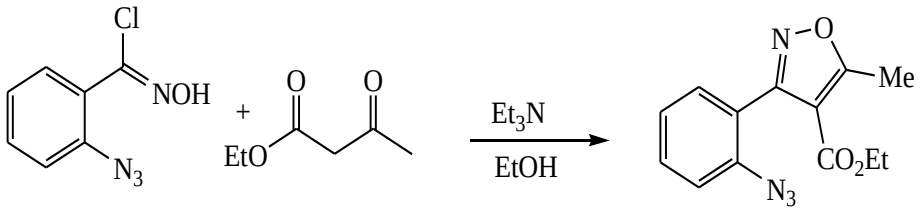



**490** **491**

**Scheme 3.111**

To a solution of compound **490** (70 mg, 0.12 mmol) in dry toluene (10 ml) was added triphenylphosphine (2 eq. 65 mg) and the mixture was stirred for 4 h at room temperature. After monitoring by TLC, which showed no reaction, the mixture was heated at reflux overnight and monitored by TLC which showed no product other than triphenylphosphine oxide confirming that the compound had decomposed at higher temperature.

### 3.5.18. Synthesis of 1-(3-(2-azidophenyl)-5-ethoxyisoxazole-4-yl)ethanone.




**352** **422** **492**

**Scheme 3.112**

To a solution of ethyl acetoacetate (330 mg, 2.54 mmol) and dry triethylamine (2 eq. 513 mg, 0.71 ml) in EtOH (10 ml) was added a solution of *o*-azidobenzohydroximoyl chloride (1 eq. 500 mg) in EtOH (20 ml) dropwise over 4-5 h under a nitrogen atmosphere and the mixture was stirred overnight. The mixture was then concentrated *in vacuo* and the crude residue was purified by flash column chromatography (PE / EtOAc : 8/1, Rf = 0.38) to give the product as yellow oil, 224 mg, 32 %.

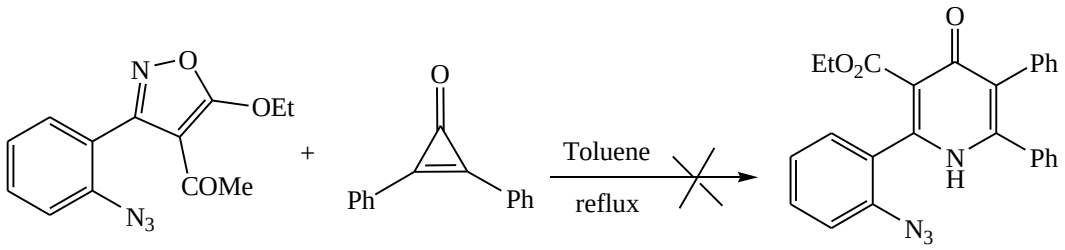
**IR: $\upsilon_{max}$ ($cm^{-1}$)** 2991 (m), 2123 (m, $N_3$), 1717 (C=O), 1604 (s), 1578 (s), 1514 (s), 1458 (s), 1310 (m), 1293 (m), 1173 9m), 1104 (m), 1018 (s), 980 (s), 889 (s), 788 (m), 756 (m).

**$^1$H NMR (400 MHz) ($CDCl_3$) δ** 7.41 (1H, td, *J*= 5.0 and 1.3 Hz, ArH), 7.30 (1H, dd, *J*= 4.9 and 1.2 Hz, ArH), 7.14-7.11 (2H, m, ArH), 4.08 (2H, q, *J*= 5.7 Hz, $CH_2$), 2.64 (3H, s, $CH_3$), 1.03 (3H, t, *J*= 5.8 Hz, $CH_3$).

**$^{13}$C NMR (100 MHz) ($CDCl_3$) δ** 174.78 (C=O), 161.56 (C), 159.76 (C), 139.07 (C), 130.84 (CH), 130.74 (CH), 124.48 (CH), 120.92 (C), 118.05 (CH), 109.77 (C), 60.38 ($CH_2$), 13.73 ($CH_3$), 13.07 ($CH_3$).

**MS. (ESI, *m/z*)**, 295.080161 $(M+Na)^+$ calculated for $C_{13}H_{12}N_4O_3Na$ and found 295.079985.

### 3.5.19. Reactivity of 1-(3-(2-azidophenyl)-5-ethoxyisoxazole-4-yl)ethanone[317].




**492** **300** **493**

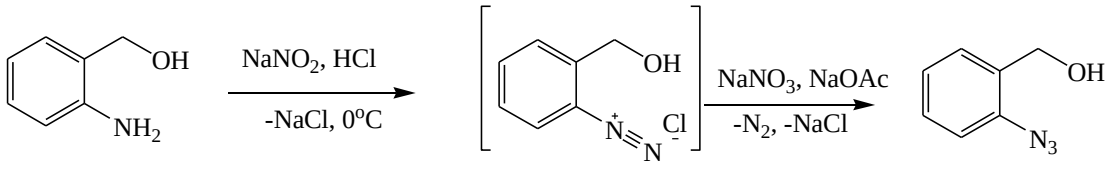
**Scheme 3.113**

To a mixture of 1-(3-(2-azidophenyl)-5-ethoxyisoxazole-4-yl)-ethanone (100 mg, 0.37 mmol) in dry toluene (10 ml) was added diphenylcyclopropenone (DPP) (76 mg, 0.37 mmol, 1 eq.) under a nitrogen atmosphere and the mixture was refluxed for 48 hours. The reaction was monitored by TLC at regular intervals but no product could be identified.

## 3.6. Synthesis of 1,3-dipoles

### 3.6.1. Synthesis of *o*-azidobenzylhydroximoyl chloride.

#### 3.6.1.1. Synthesis of *o*-azidobenzyl alcohol [247]




**509** **510** **511**

**Scheme 3.114**

To a solution of *o*-aminobenzyl alcohol (5 g, 40.60 mmol, 1 eq.) in concentrated hydrochloric acid ( 40 ml) and water ( 40 ml) at 0 $^{o}$C was added, with stirring, a solution of sodium nitrite (2.8 g, 41.16 mmol, 1.01 eq.) in water (10 ml), dropwise over 10 minutes. Stirring was continued for a further hour and the resulting mixture, maintaining its temperature at 0 $^{o}$C, was added dropwise over an hour to an ice-cooled mixture of sodium azide (2.65 g, 40.755 mmol, 1 eq.) and sodium acetate (37.5 g) in water (75 ml). The white precipitates formed were filtered, washed thoroughly with water (3 x 50 ml) and dried *in vacuo* for an hour to give *o*-azidobenzyl alcohol (5.3 g, 57 % yield) as a white crystalline solid, m.p.: 50-51 $^{o}$C [247].

**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3600 (m), 3404 (bm), 2933 (w), 2881 (w), 2127 (s), 1585 (m), 1490 (s), 1452 (m), 1282 (s), 1008 (m), 756 (s), 669 (s).

**$^{1}$H NMR δ (400 MHz, $d_6$-DMSO):** 7.47 (1H, dd, J= 7.5, 0.8, Ar H), 7.35 ( 1H, td, J= 7.6, 1.6, Ar H), 7.26-7.16 (2H, m, 2x Ar H), 5.21 (1H, s, br, OH), 4.44 (2H, s, $CH_2$).

**$^{13}$C NMR δ (100 MHz, $d_6$-DMSO):** 139.0 (q), 133.3 (q), 128.1 ( CH), 127.9 (CH), 118 (CH), 58.3 ($CH_2$).

Data identical to literature [247].

### 3.6.1.2. Synthesis of *o*-azidobenzaldehyde[247]


**511** **512**

**Scheme 3.115**

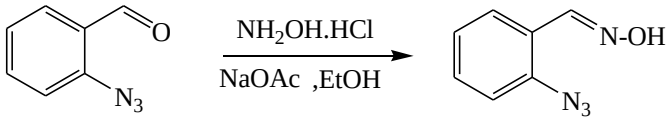
To *o*-azidobenzyl alcohol (3 g, 19.72 mmol, 1 eq.) in anhydrous dichloromethane (25 ml) was added freshly prepared pyridinium chlorochromate (20 g, 92.76 mmol, 4.7 eq. ) and the whole was stirred vigorously for 3 hours with occasional cooling in a water bath ( exothermic reaction). The dark reaction mixture was quenched with ether (100 ml) and the supernatant liquid was removed by decantation. The black tar residue was washed thoroughly with ethyl acetate (5 x 50 ml) and the combined organic layers were collected, dried ($MgSO_4$), and filtered under gravity. Evaporation of the solvent gave a brown oil, which crystallised on cooling to give *o*-azidobenzaldehyde (2.8 g, 97 % yield) as brown needles, m.p. 33-35 $^oC$.

**$^1$H NMR δ (400 MHz, $CDCl_3$):** 8.84, (1H, s), 8.07 (1H, dd, J= 6.4, 1.2, Ar H), 7.08-7.20 (2H, m, 2x Ar H), 7.41 ( 1H, td, J= 7.1, 1.5, Ar H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 156.5 (C=O), 139.5 (CH), 131.6 (CH), 127.2 (CH), 124.5 (CH), 124.2 (C), 117.9 (C).

The data is identical to literature [247].

### 3.6.1.3. Synthesis of *o*-azidobenzaldoxime[247]




**512** **513**

**Scheme 3.116**

To a mixture of hydroxylamine hydrochloride (6.367 g, 0.88 mmol, 4 eq.) and sodium acetate (11 g) in ethanol (150 ml) was added, at room temperature with vigorous stirring, *o*-azidobenzaldehyde (3.366 g, 0.022 mmol, 1 eq). The reaction mixture was stirred for 5 hours, filtered *in vacuo* to remove the precipitates and the solvent evaporated off. The crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 5:1) to yield *o*-azidobenzaldoxime (2.27 g, 61 % yield) as pale yellow needles, m.p: 100-102 $^{o}$C.

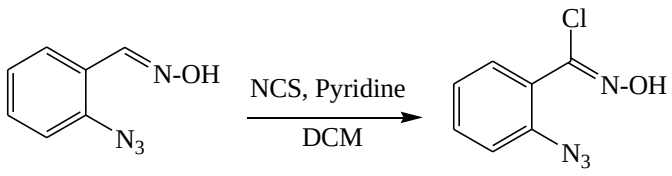
**IR: $\upsilon_{max}$ (cm$^{-1}$)** 3576 (m), 3390 (bm), 2934 (m), 2127 (s), 1597 (m), 1573 (m), 1489 (s), 1455 (m), 1290 (s), 1050 (m), 972 (m), 770 (s), 669 (s).

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.25 (1H, s, br, OH), 8.40 (1H, s, HC=NOH), 7.73 (1H, dd, J= 7.8, 1.5, Ar H), 7.46-7.38 (1H, m, ArH), 7.19-7.11 (2H, m, 2x Ar H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 146.1 (HC=NOH), 138.5 (q), 131.2 (CH), 127.2 (CH), 125.0 (CH), 123.2 (q), 118.6 (CH).

The data is identical to literature[247].

### 3.6.1.4. Synthesis of *o*-azidobenzohydroxyimoyl chloride[247]




**513** **352**

**Scheme 3.117**

To a solution of N-chlorosuccinimide (1.25 g, 9.343 mmol, 1.01 eq) in anhydrous dichloromethane (10 ml) and pyridine (0.1 ml, d= 0.978) was added o-azidobenzaldoxime (1.5 g, 9.25 mmol, 1 eq) at room temperature with stirring. The reaction mixture was left stirring overnight, then it was concenterated *in vacuo* and crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 4:1) to yield *o*-azidobenzohydroxyimoyl chloride (1.52 g, 76 % yield) as a brown crystalline solid, m.p: 80-82 $^{o}$C [247].

**IR: $\upsilon_{max}$ ($cm^{-1}$)** 3400 (bw), 2920 (w), 2131 (s), 1597 (s), 1578 (m), 1459 (m), 1420 (m), 1300 (s), 1082 (w), 991 (w), 755 (s), 668 (m).

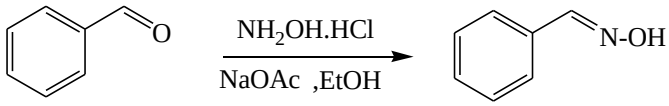
**$^1$H NMR δ (400 MHz, $CDCl_3$):** 9.71 (1H, s, br, OH), 7.55 (1H, dd, J= 7.7, 1.1, ArH), 7.47 (1H, dt, J= 7.8, 1.4, ArH), 7.30-7.16 (2H, m, 2xArH).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 138.3 (q, C=N), 136.3 (q), 131.6 (CH), 131.2 (CH), 124.8 (CH), 124.7 (q), 119.0 (CH).

The data is identical to that previously reported [247].

## 3.6.2. Synthesis of benzohydroximoyl chloride.

### 3.6.2.1. Synthesis of benzaldoxime[247]




**514** **515**

**Scheme 3.118**

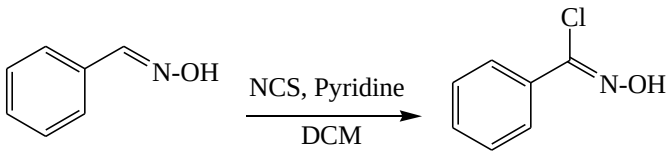
To a mixture of hydroxylamine hydrochloride (13.1 g, 0.19 mmol, 4 eq.) and sodium acetate (20 g) in ethanol (100 ml) was added, at room temperature with vigorous stirring, benzaldehyde (5 g, 47.16 mmol, 1 eq). The reaction mixture was stirred for 5 hours, filtered *in vacuo* to remove the precipitates and the solvent was evaporated off. The crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 5:1) to yield benzaldoxime (6.57 g, 87 % yield) as pale yellow oil.

**$^1$H NMR δ (400 MHz, $CDCl_3$):** 10.01 (1H, s, br, OH), 8.26 (1H, s, CH=NOH), 7.63 (2H, dd, J= 6.8 and 1.1, 2x Ar H), 7.38-7.48 (3H, m, ArH).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 150.3 (CH=NOH), 131.8 (Cq), 130.7 (CH), 128.9 (CH), 127.4 (CH).

The data is identical to that previously reported [247].

### 3.6.2.2. Synthesis of benzohydroxyimoyl chloride[247]




**515** **516**

**Scheme 3.119**

To a solution of N-chlorosuccinimide (2.24 g, 16.7 mmol, 1eq) in anhydrous dichloromethane (10 ml) and pyridine (0.1 ml, d= 0.978) was added benzaldoxime (2 g, 16.7 mmol, 1 eq) at room temperature with stirring. The reaction mixture was left stirring overnight, then it was concentrated *in vacuo* and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 4:1) to yield benzohydroxyimoyl chloride (1.7 g, 68 % yield) as a brown oil.

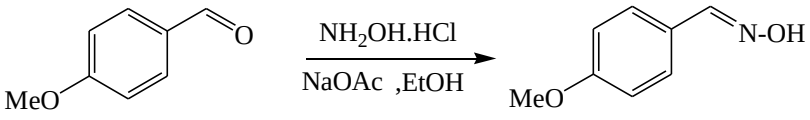
**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.40 (1H, s, br, OH), 7.82 (2H, dd, J= 6.8 and 1.1, 2x Ar H), 7.38-7.48 (3H, m, ArH).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 140.2 (C=NOH), 132.3 (q), 130.6 (CH), 128.8 (CH), 127.5 (CH).

The data is identical to that previously reported [247].

## 3.6.3. Synthesis of *p*-methoxybenzohydroximoyl chloride.

### 3.6.3.1. Synthesis of *p*-methoxybenzaldoxime[247]




**517** **518**

**Scheme 3.120**

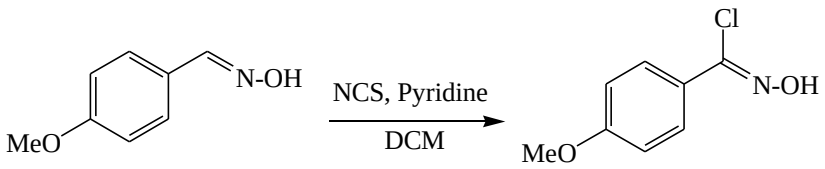
To a mixture of hydroxylamine hydrochloride (4.09 g, 58.8 mmol, 4 eq.) and sodium acetate (11 g) in ethanol (100 ml) was added, at room temperature with vigorous stirring, *p*-methoxybenzaldehyde (2 g, 14.70 mmol, 1 eq). The reaction mixture was stirred for 5 hours, filtered *in vacuo* to remove the precipitates and the solvent was evaporated off. The crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 5:1) to yield *p*-methoxybenzaldoxime (2.72 g, 82 % yield) as a brown solid.

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.23 (1H, s, br, OH), 8.15 (1H, s, CH=NOH), 7.53 (2H, d, J= 8.7, 2x Ar-H), 6.92 (2H, d, J= 8.8, 2xAr-H), 3.8 (3H, s, $OCH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 161.1 (C), 149.8 (C=N), 128.6 (CH), 114.3 (CH), 113.7 (C), 55.3 ($OCH_3$).

The data is identical to literature [247].

### 3.6.3.2. Synthesis of *p*-methoxybenzohydroxyimoyl chloride[247]




**518** **346**

**Scheme 3.121**

To a solution of N-chlorosuccinimide (2.56 g, 19.20 mmol, 1.01 eq) in anhydrous dichloromethane (10 ml) and pyridine (0.1 ml, d= 0.978) was added *p*-methoxybenzaldoxime (2.9 g, 19.20 mmol, 1 eq) at room temperature with stirring. The reaction mixture was left stirring overnight, then it was concentrated *in vacuo* and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 4:1) to yield *p*-methoxybenzohydroxyimoylchloride (2.7 g, 77 % yield) as a brown solid.

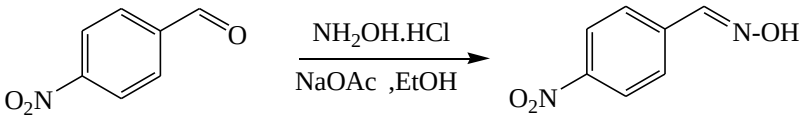
**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 9.18 (1H, s, br, OH), 7.50 (2H, d, J= 7.8, 2x Ar-H), 6.97 (2H, dd, J= 6.4 and 2.6, 2xAr-H), 3.8 (3H, s, $OCH_3$).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 161.6 (C), 130.0 (C=N), 125.6 (CH), 114.4 (CH), 113.9 (C), 55.4 ($OCH_3$).

Data was identical to literature[247].

## 3.6.4. Synthesis of *p*-nitrobenzohydroximoyl chloride.

### 3.6.4.1. Synthesis of *p*-nitrobenzaldoxime[247]




**519** **520**

**Scheme 3.122**

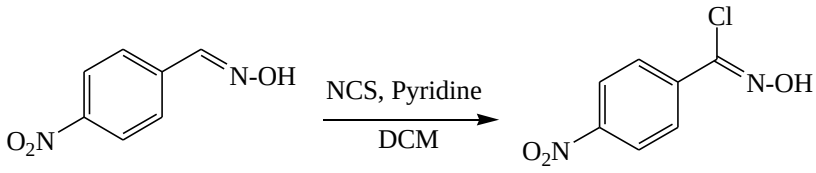
To a mixture of hydroxylamine hydrochloride (3.68 g, 52.98 mmol, 4 eq.) and sodium acetate (11 g) in ethanol (150 ml) was added, at room temperature with vigorous stirring, *p*-nitrobenzaldehyde (2 g, 13.24 mmol, 1 eq). The reaction mixture was stirred for 5 hours, filtered *in vacuo* to remove the precipitates and the solvent was evaporated off. The crude product was purified by flash column chromatography ( eluent: PE:EtOAc/ 5:1) to yield *p*-nitrobenzaldoxime (1.97 g, 90 % yield) as pale yellow needles, m.p: 100-102 $^{o}$C.

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 8.28 (2H, d, J= 8.8, 2x Ar-H), 8.22 (1H, s, CH=NOH), 8.05 (1H, s, br, OH), 7.78 (2H, d, J= 8.8, 2x Ar-H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 148.4 (C=N), 148.3 (C), 138.1 (C), 127.6 (CH), 124.0 (CH).

Data was identical to that previously reported[247].

### 3.6.4.2. Synthesis of *p*-nitrobenzohydroxyimoyl chloride[247]




**520** **521**

**Scheme 3.123**

To a solution of N-chlorosuccinimide (1.76 g, 13.13 mmol, 1 eq) in anhydrous dichloromethane (10 ml) and pyridine (0.1 ml, d= 0.978) was added *p*-nitrobenzaldoxime (2.19 g, 13.13 mmol, 1 eq) at room temperature with stirring. The reaction mixture was left stirring overnight, then it was concentrated *in vacuo* and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 4:1) to yield *p*-nitrobenzohydroxyimoyl chloride (1.2 g, 45 % yield) as a yellow crystalline solid.

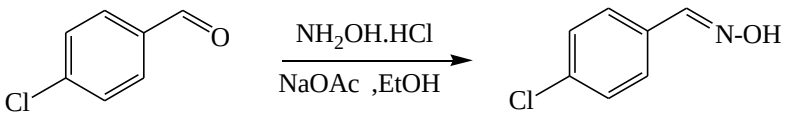
**$^1$H NMR δ (400 MHz, $CDCl_3$):** 8.42 (1H, s, br, OH), 8.38 (2H, d, J= 7.4, 2x Ar-H), 7.92 (2H, d, J= 7.4, 2x Ar-H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 133.4 (CH), 130.5 (C), 128.3 (C), 124.3 (CH), 124.0 (C).

Data was identical to literature[247].

## 3.6.5. Synthesis of *p*-chlorobenzohydroximoyl chloride.

### 3.6.5.1. Synthesis of *p*-chlorobenzaldoxime[247]




**522** **523**

**Scheme 3.124**

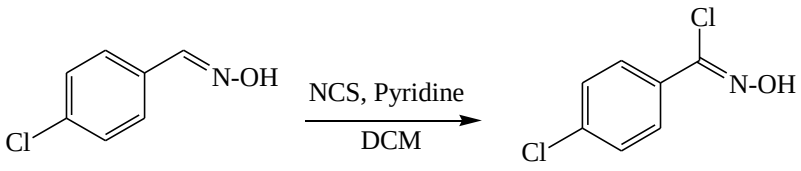
To a mixture of hydroxylamine hydrochloride (3.95 g, 56.93 mmol, 4 eq.) and sodium acetate (11 g) in ethanol (100 ml) was added, at room temperature with vigorous stirring, *p*-chlorobenzaldehyde (2 g, 14.23 mmol, 1 eq). The reaction mixture was stirred for 5 hours, filtered *in vacuo* to remove the precipitates and the solvent was evaporated off. The crude product was purified by flash column chromatography ( eluent: PE:EtOAc/ 5:1) to yield *p*-chlorobenzaldoxime (2.09 g, 95 % yield) as white needles.

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 8.56 (1H, s, br, OH), 8.14 (1H, s, CH=NOH), 7.54 (2H, d, J= 8.5, 2x Ar-H), 7.38 (2H, d, J= 8.5, 2x Ar-H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 149.3 (C=N), 136.0 (C), 130.3 (C), 129.1 (CH), 128.2 (CH).

The data is identical to that previously reported[247].

### 3.6.5.2. Synthesis of *p*-chlorobenzohydroxyimoyl chloride[247]




**523** **524**

**Scheme 3.125**

To a solution of N-chlorosuccinimide (1.97 g, 14.77 mmol, 1 eq) in anhydrous dichloromethane (10 ml) and pyridine (0.1 ml, d= 0.978) was added *p*-chlorobenzaldoxime (2.29 g, 14.77 mmol, 1 eq) at room temperature with stirring. The reaction mixture was left stirring overnight, then it was concentrated *in vacuo* and crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 4:1) to yield *p*-chlorobenzohydroxyimoyl chloride (2.4 g, 80 % yield) as a white crystalline solid.

**$^{1}$H NMR δ (400 MHz, $CDCl_3$):** 8.32 (1H, s, br, OH), 7.79 (2H, d, J= 8.7, 2x Ar-H), 7.40 (2H, d, J= 8.8, 2x Ar-H).

**$^{13}$C NMR δ (100 MHz, $CDCl_3$):** 139.3 (C=N), 136.7 (C), 130.8 (C), 128.8 (CH), 128.4 (CH).

Data as reported in literature[247].

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